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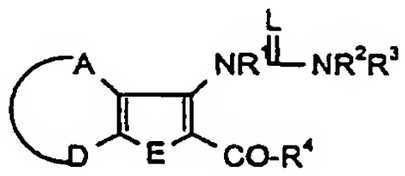

(I)

(57) Abstract

The invention relates to olighydroxyl 3–urea–benzofurane– and pyridofurane– derivatives of general formula (I), their preparation and their use in medicaments for the treatment of inflammatory processes.

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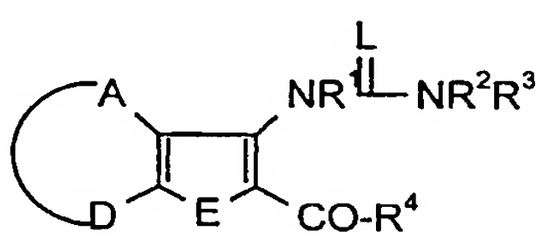
OLIGOHYDROXYL SUBSTITUTED BENZOFURAN-3-YL AND PYRIDOFURANYLUREA DERIVATIVES AS PHOSPHODIESTERASE IV INHIBITORS

The invention relates to oligohydroxyl 3-urea-benzofurane- and -pyridofurane-derivatives, processes for their preparation and their use in medicaments.

It is known that the NADPH oxidase of phagocytes is the physiological source to the superoxide radical anion and reactive oxygen species derived therefrom which are important in the defence against pathogens. Moreover, both inflammatory (e.g. TNFα, IL-1 or IL-6) and anti-inflammatory cytokines (e.g. IL-10) play a pivotal role in host defence mechanisms. Uncontrolled production of inflammatory mediators can lead to acute and chronic inflammation, tissue damage, multi-organ failures and to death. It is additionally known that elevation of phagocyte cyclic AMP leads to inhibition of oxygen radical production and that this cell function is more sensitive than others such as aggregation or enzyme release.

Benzofuran derivatives having phosphodiesterase IV (PDE IV)-inhibiting action are described in the publication EP 0 731 099 A2. The reference describes only single-hydroxyl substituted derivatives, however. In order to provide alternative compounds of similar or improved PDE IV-inhibitory activity the present invention relates to oligohydroxyl 3-urea-benzofurane- and -pyridofurane-derivatives of the general formula (I)



(I)

in which

A and D including the double bond connecting them together form a phenyl-, pyridyl-, pyrimidyl, pyridazinyl-, pyrazinyl- or thienyl-ring, which is substituted by a group of a formula -OR^5

wherein

R^5 denotes straight-chain or branched alkyl having 1 to 15 carbon atoms, which is substituted difold to fivefold by hydroxyl or by straight-chain oder branched alkoxy having 1 to 6 carbon atoms and wherein alkyl is optionally substituted by straight-chain or branched alkoxycarbonyl having 1 to 6 carbon atoms, halogen, carboxyl, (C_3-C_8)-cycloalkyl or by phenyl, which is optionally substituted monofold to fivefold by nitro, halogen or phenyl,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms, an aminoprotecting group or a group of the formula -CO-R^6

in which

R^6 denotes straight chain or branched alkoxy having 1 to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cycloalkyl having 3, 4, 5 or 6 carbon atoms, straight chain or branched alkyl, alkoxycarbonyl or alkenyl each having 1 to 8 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a 5-, 6- or 7-membered saturated heterocycle optionally having a further oxygen atom,

R^4 represents aryl having 6 or 10 carbon atoms or

represents a 5-, 6- or 7-membered, aromatic, saturated or unsaturated heterocycle, which can contain 1 to 3 oxygen, sulphur and/or nitrogen atoms as heteroatoms or a residue of a formula $-NR^7$,

wherein

R^7 denotes hydrogen or straight-chain or branched alkyl or alkoxycarbonyl each having 1 to 6 carbon atoms,

and to which further a benzene ring can be fused and wherein aryl and/or the heterocycle are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having 1 to 6 carbon atoms or by straight-chain or branched alkyl having 1 to 5 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having 1 to 4 carbon atoms or by a group of formula $-NR^8R^9$, $-SR^{10}$, $-(NH)_a-SO_2R^{11}$ or $-O-SO_2R^{12}$,

in which

R^8 and R^9 are identical or different and denote hydrogen or a straight-chain or branched alkyl having 1 to 4 carbon atoms,

or

R^8 denotes hydrogen

and

R^9 denotes straight-chain or branched acyl having 1 to 6 carbon atoms

R^{10} denotes hydrogen or straight-chain or branched alkyl having 1 to 4 carbon atoms,

a denotes a number 0 or 1,

R^{11} and R^{12} are identical or different and represent straight-chain or branched alkyl having 1 to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having 1 to 4 carbon atoms,

L represents an oxygen or sulfur atom

and salts thereof.

The oligohydroxyl substituted 3-urea-benzofurane- and -pyridofurane-derivatives according to the invention can also be present in the form of their salts and pyridinium oxide. In general, salts with organic or inorganic bases or acids may be mentioned here.

Physiologically acceptable salts are preferred in the context of the present invention. Physiologically acceptable salts of the oligohydroxyl substituted 3-urea-benzofurane and -pyridofurane-derivatives can be metal or ammonium salts of the substances according to the invention, which contain a free carboxylic group. Those which are particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

Physiologically acceptable salts can also be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts here are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid. Preferred pyridinium salts are salts in combination with halogen.

The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemate forms, as well as the diastereomer mixtures and individual diastereomers. The racemate forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

Heterocycle in general represents a 5- to 7-membered, aromatic, saturated or unsaturated, preferably 5- to 6- membered, aromatic saturated or unsaturated ring which can contain 1 to 3 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further aromatic rings can be fused.

The following are mentioned as preferred: thienyl, furyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxazolyl, cinnolyl, thiazolyl, dihydrothiazolyl, benzothiaazolyl, isothiazolyl, benzisothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, indolyl, morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, oxazolinyl or triazolyl.

Preferred compounds of the general formula (I) are those

in which

A and D, including the double bond connecting them form together a phenyl-, pyridyl- or pyrimidyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having 1 to 14 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or isopropoxycarbonyl, fluorine, chlorine, cyclopentyl, cyclohexyl or by phenyl, which is optionally substituted monofold to fivefold by nitro, fluorine or chlorine,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms or a group of the formula $-CO-R^6$

in which

R^6 denotes straight chain or branched alkoxy having 1 to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having 1 to 4 carbon atoms, or

or

R^2 and R^3 together with the nitrogen atom form a pyrrolidinyl-, piperidinyl- or morpholinyl-ring,

and

R^4 represents phenyl, pyridyl or thienyl, wherein all rings are optionally mono- substituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having 1 to 3 carbon atoms, or by methyl, ethyl, n-propyl or isopropyl which are optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having 1 to 3 carbon atoms

L represents an oxygen or sulfur atom,

and salts thereof.

Particularly preferred compounds of the general formula (I) are those

in which

A and D, including the double bond connecting them form together a phenyl- or pyridyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having 1 to 11 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by methoxycarbonyl, cyclohexyl, fluorine or by phenyl, which is optionally substituted monofold to fivefold by nitro or fluorine,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, methyl, ethyl, n-propyl or isopropyl or a group of the formula -CO-R^6,

in which

R^6 denotes methoxy, ethoxy, n-propoxy or isopropoxy,

R^2 and R^3 represent hydrogen,

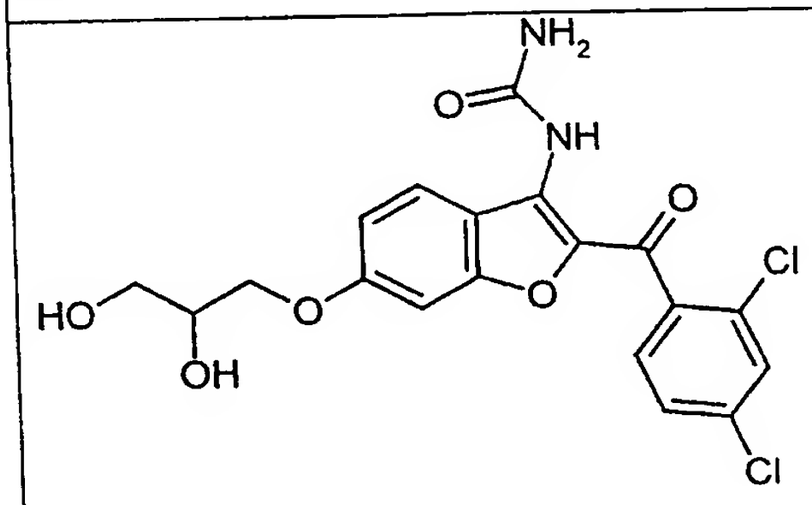
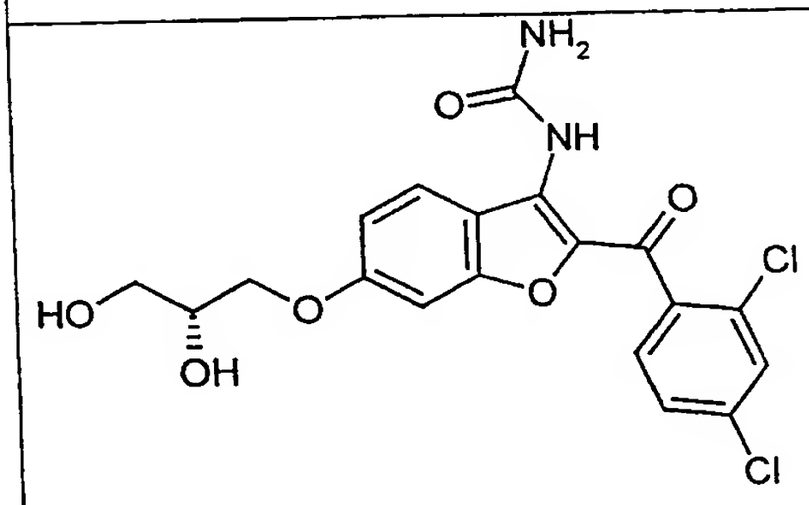
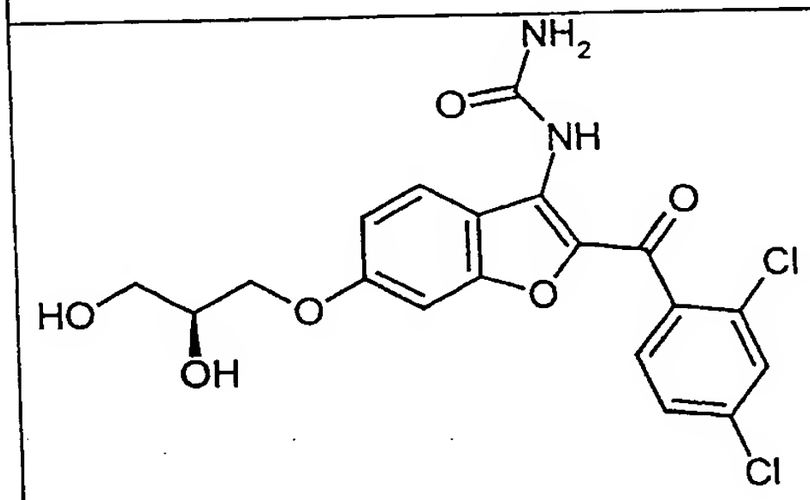
R^4 represents phenyl, pyridyl or thienyl, which are optionally up to trifold substituted by identical or different substituents from the series chlorine or methyl,

L represents an oxygen atom,

and salts thereof.

Very particularly preferred compounds of the general formula (I) are those, which are shown in table A:

Table A:

Structure

 R-ENANTIOMER
 S-ENANTIOMER

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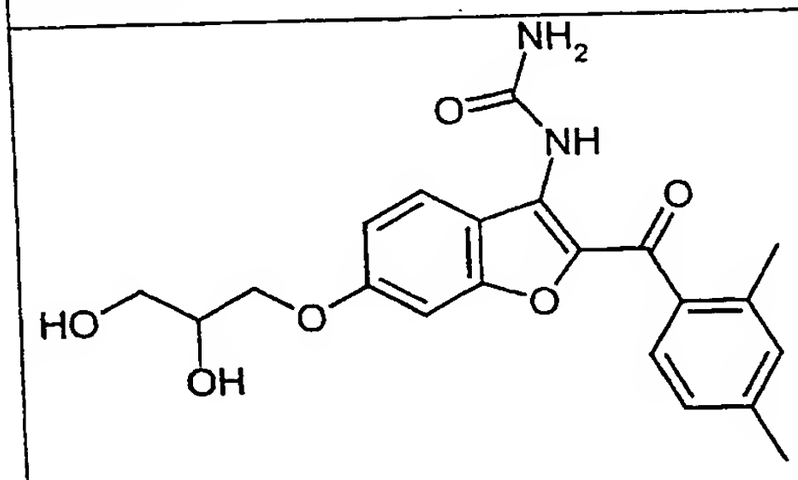
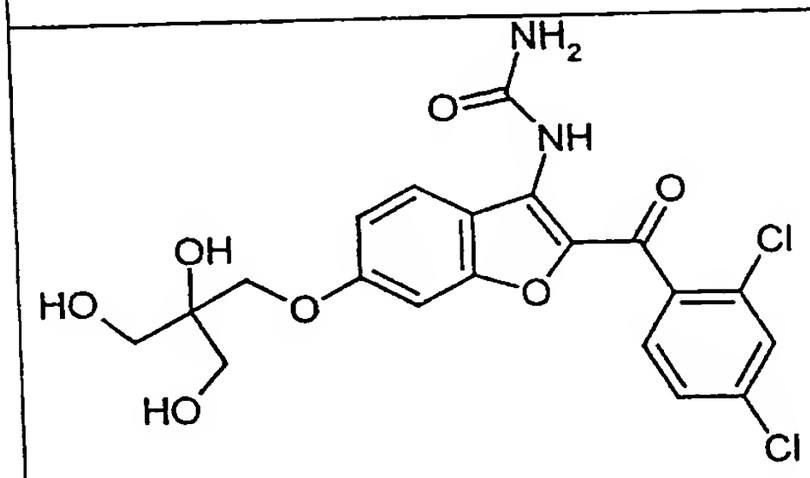
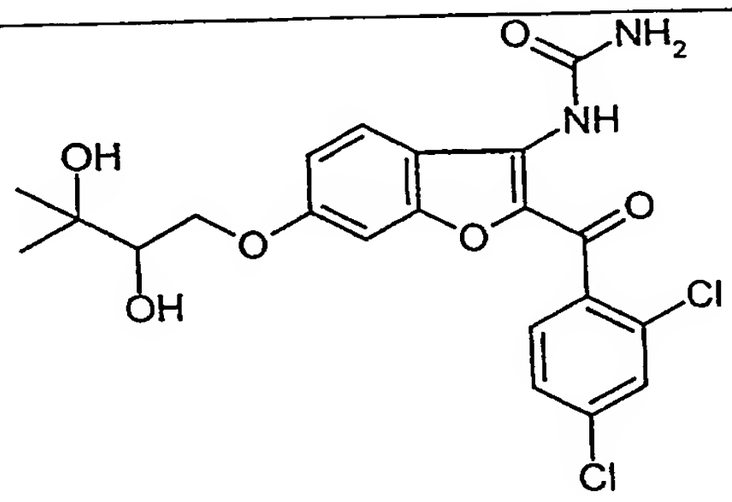
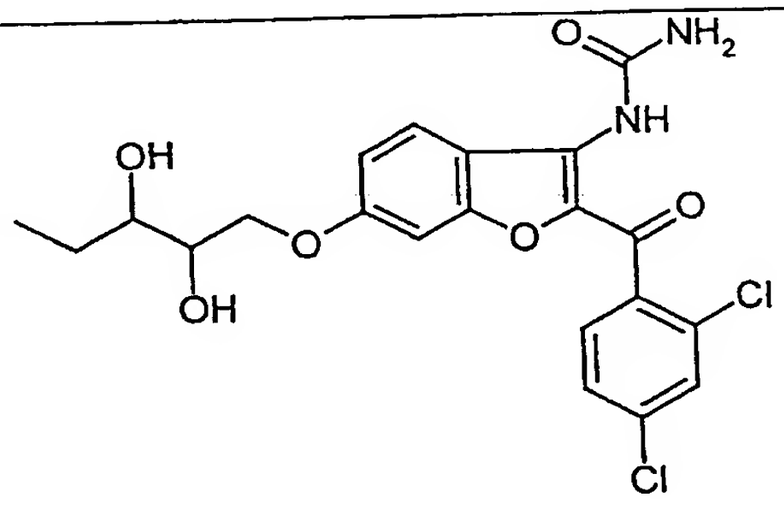

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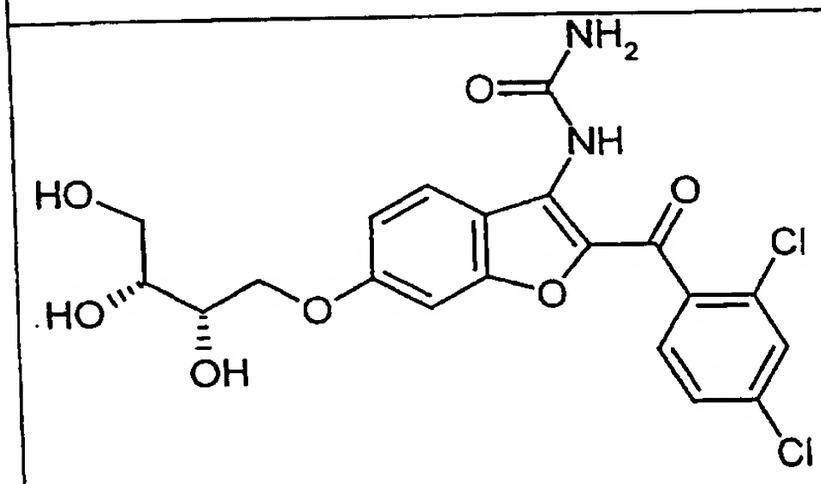
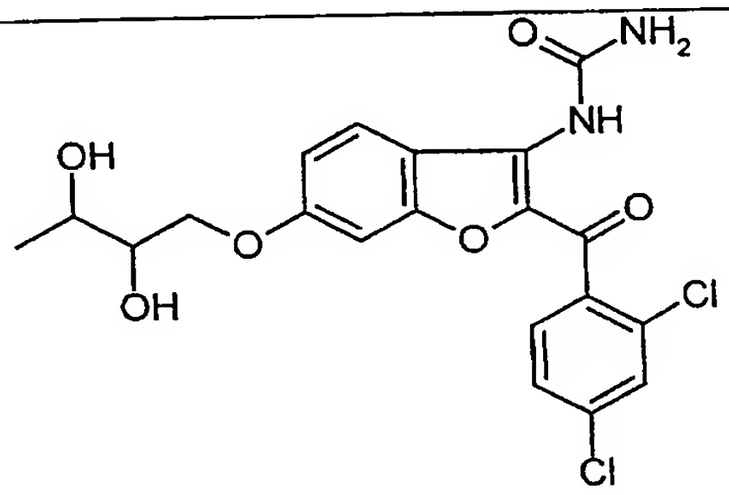
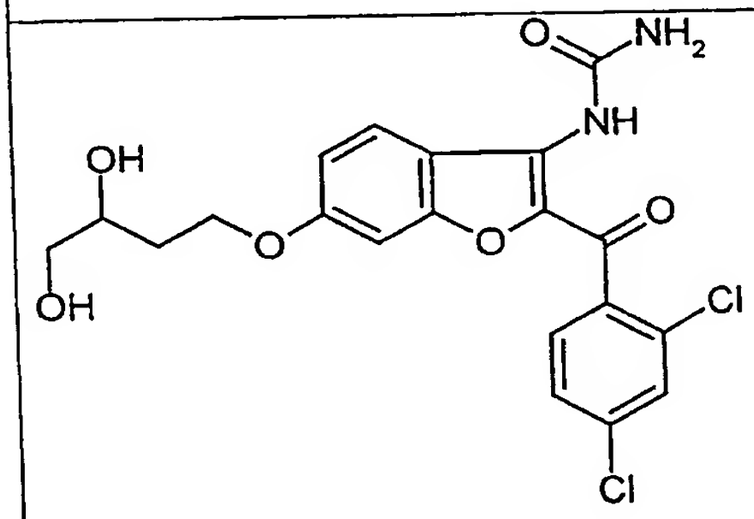
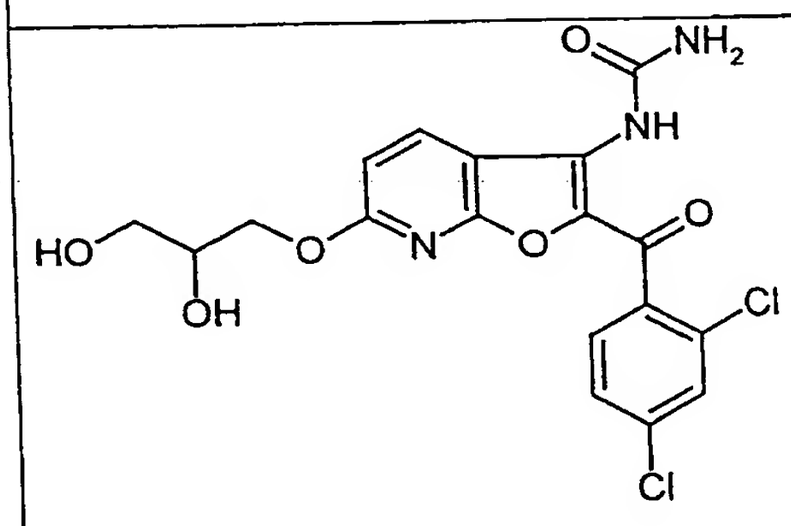

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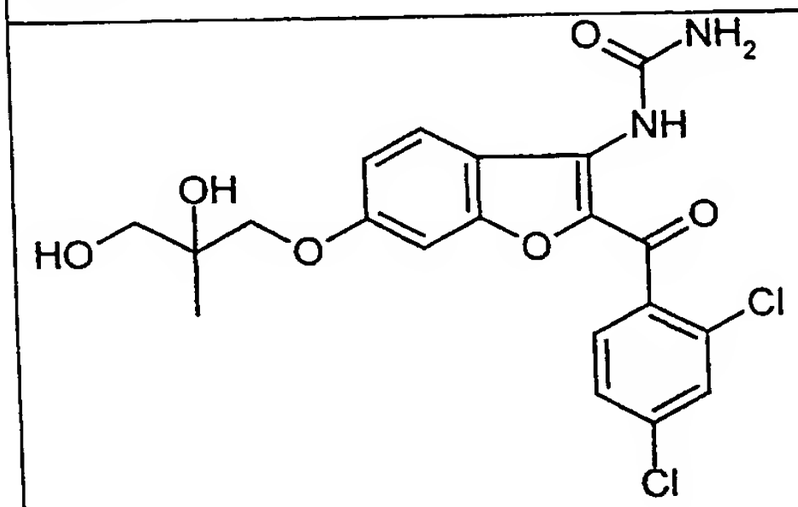
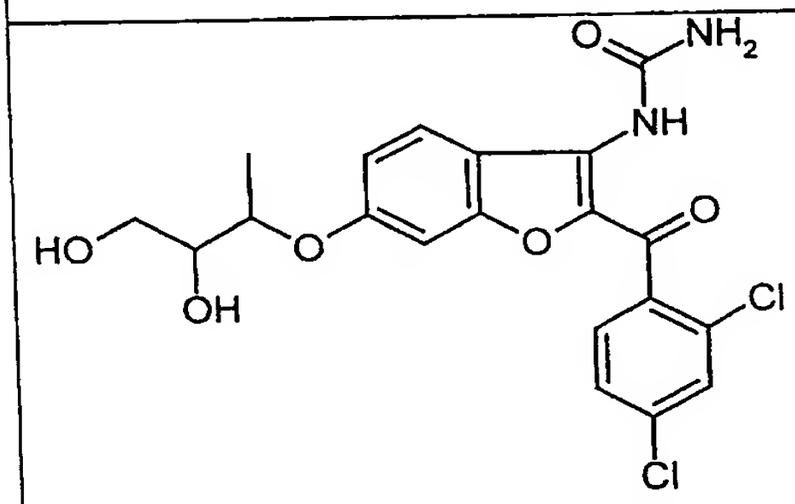
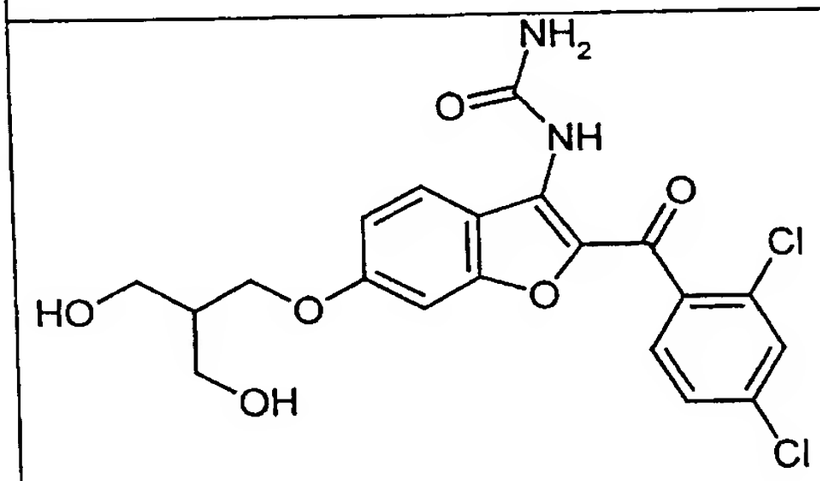
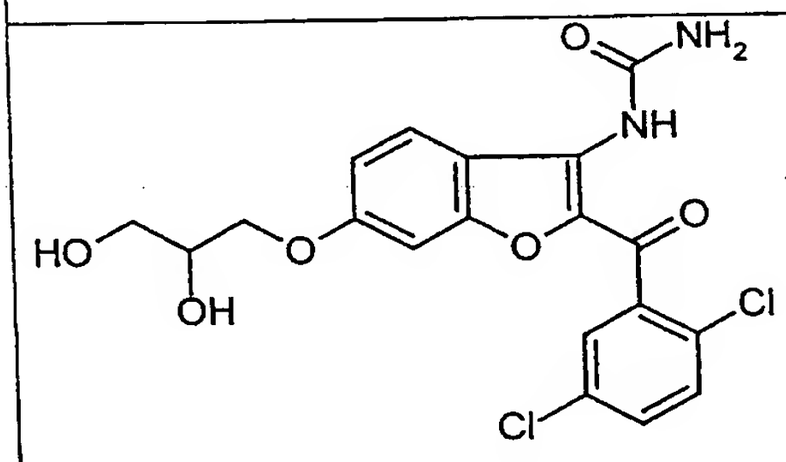

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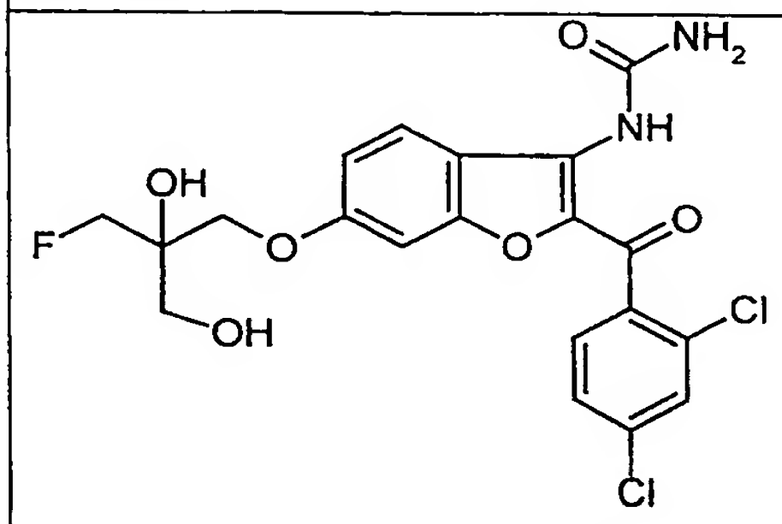
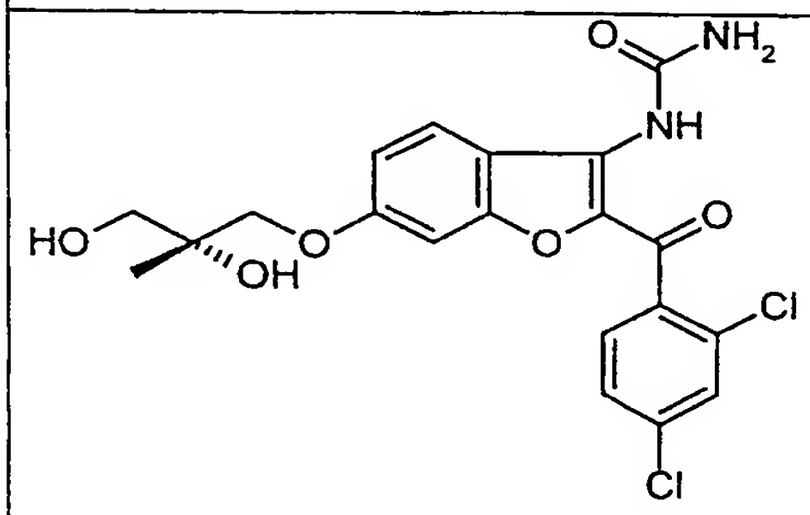
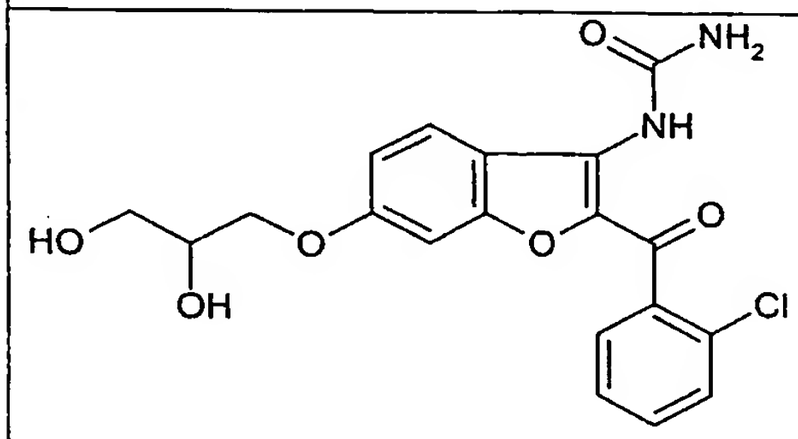
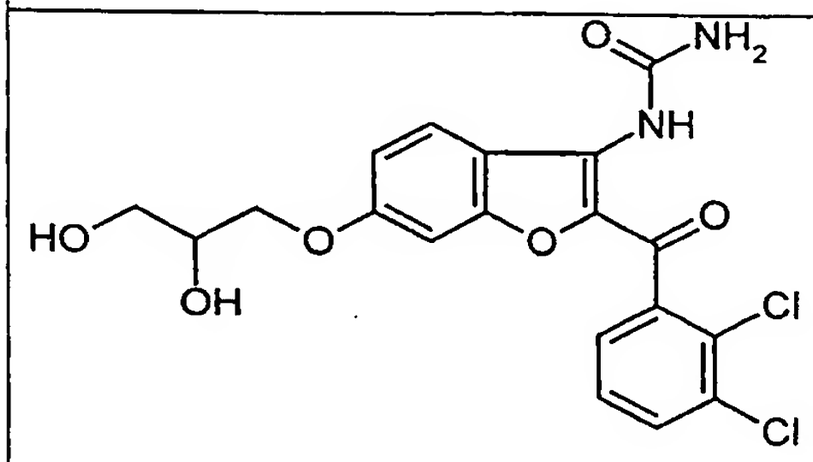

 R-ENANTIOMER



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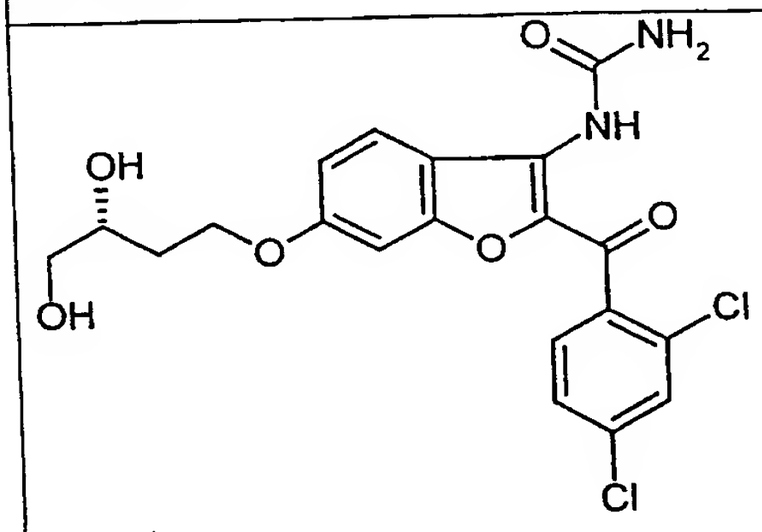
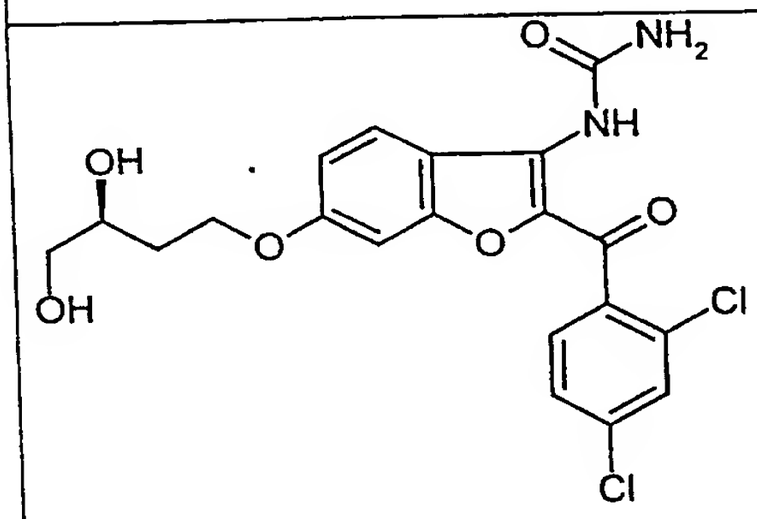
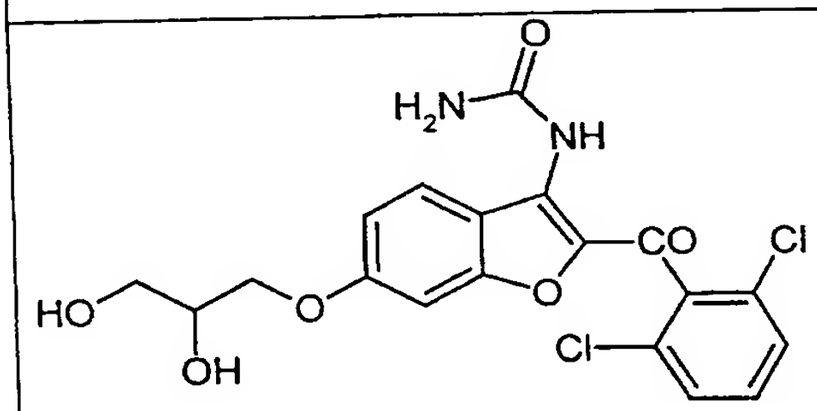
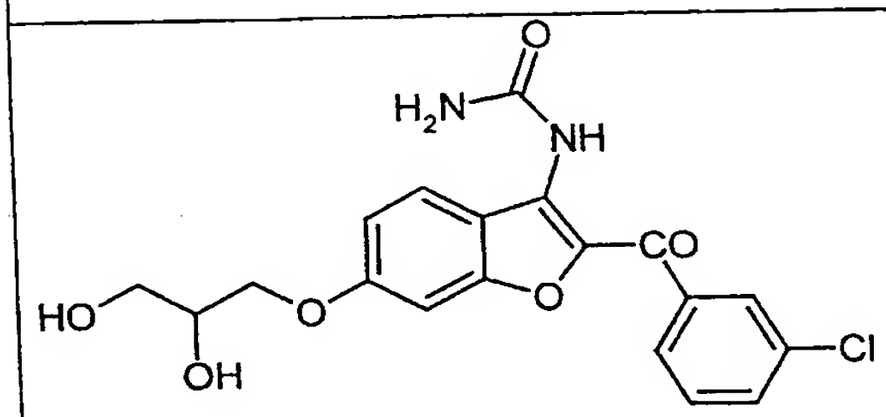

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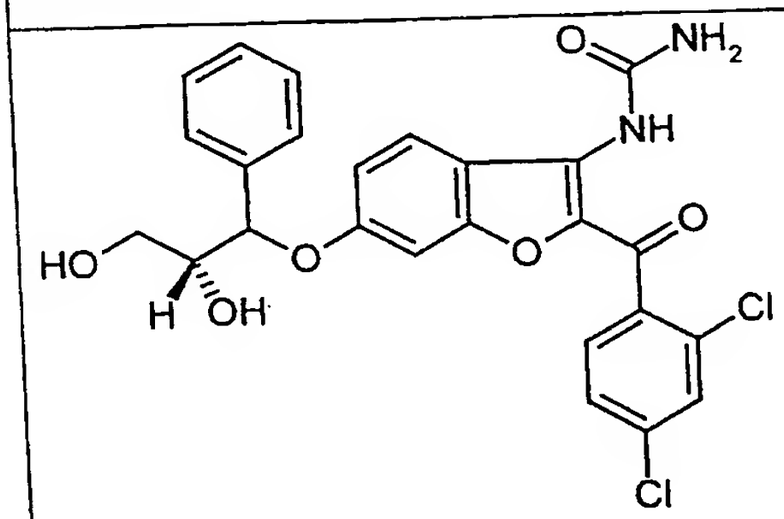
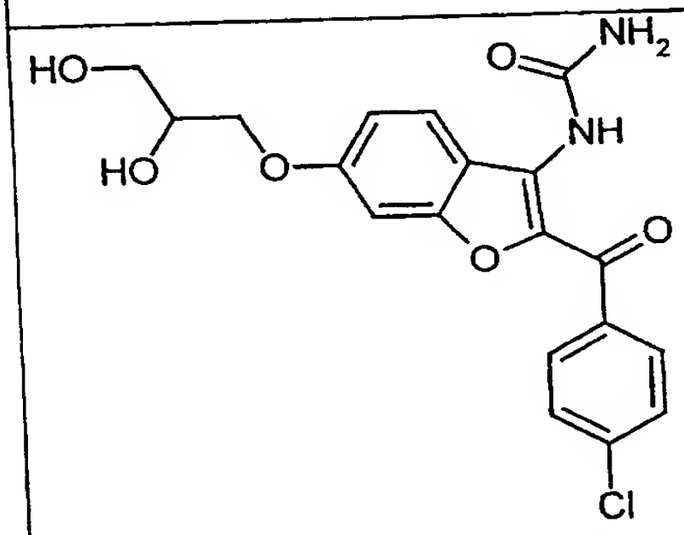
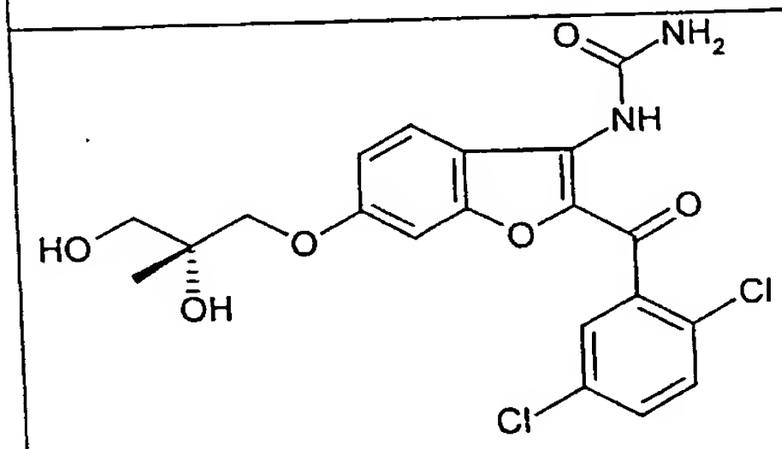
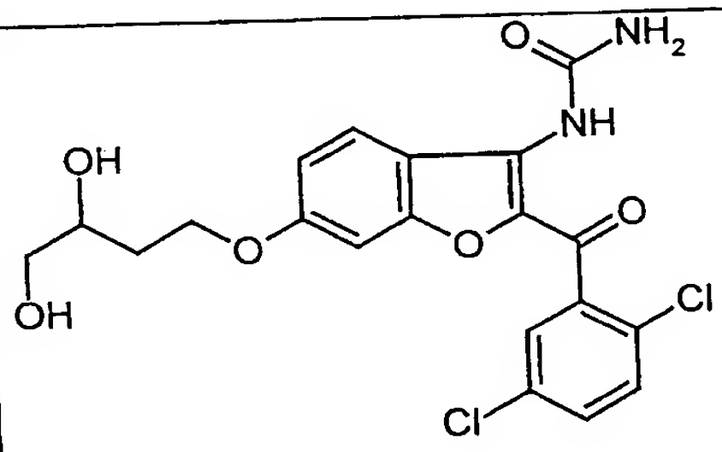


 R-ENANTIOMER


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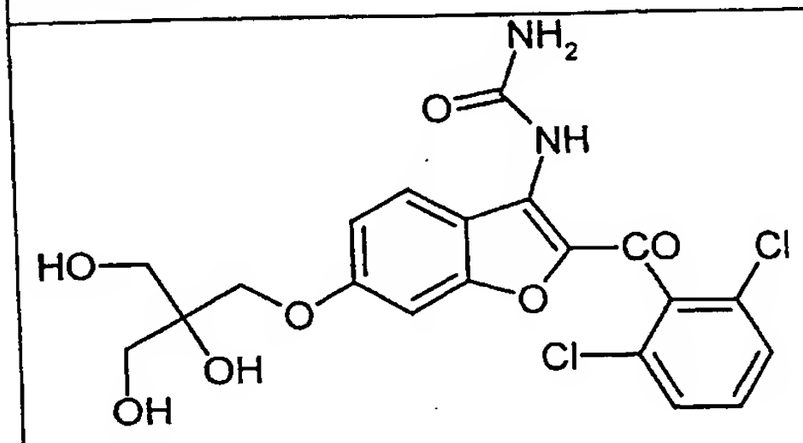
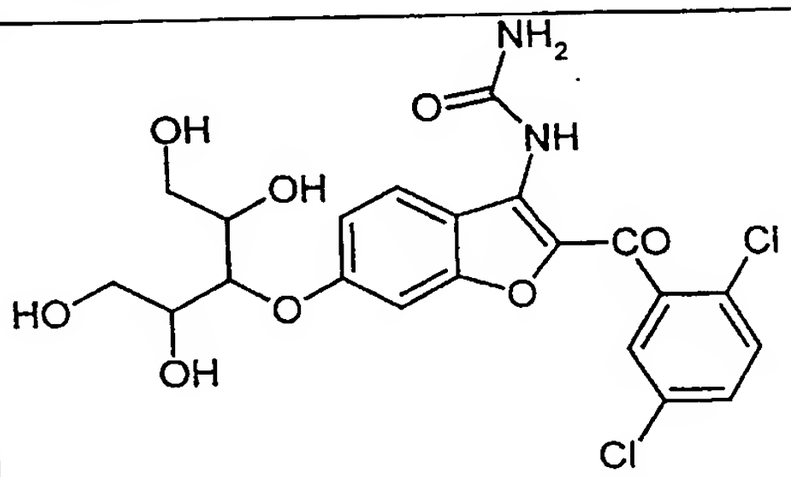
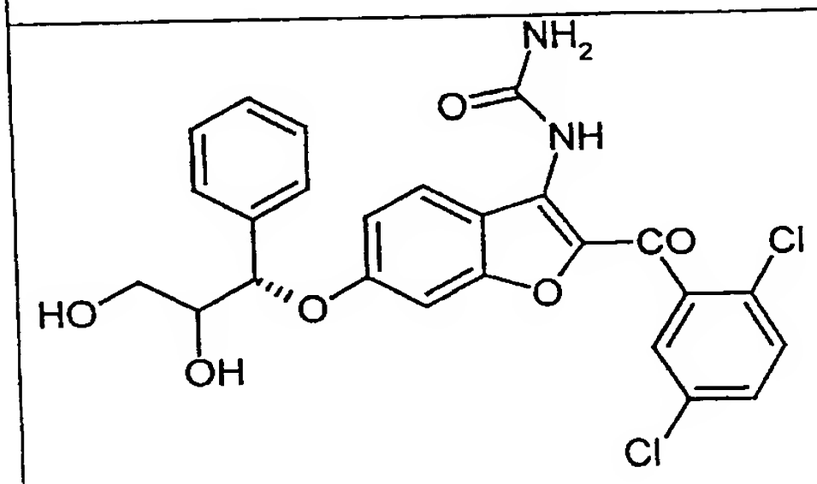
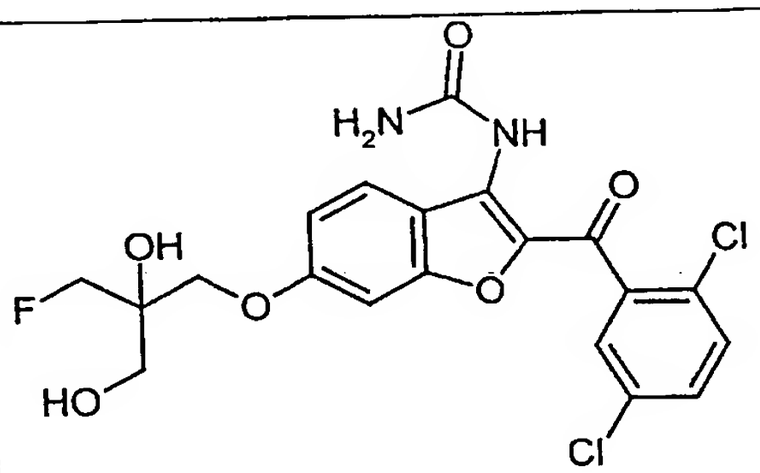

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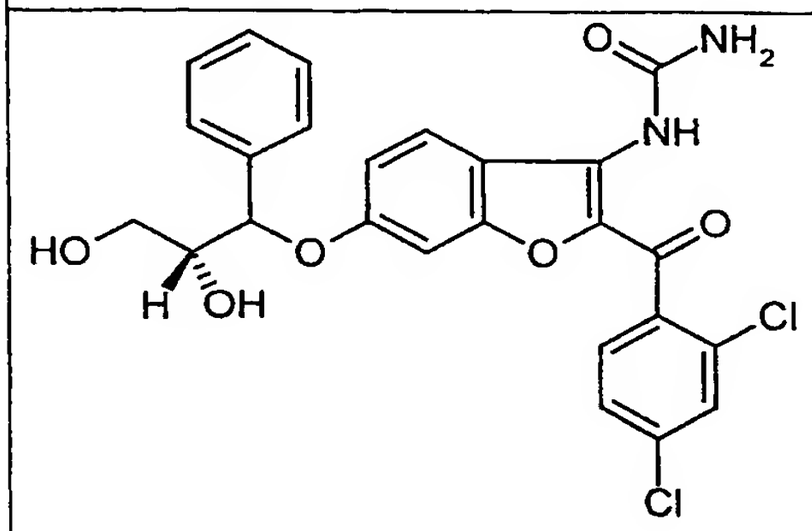
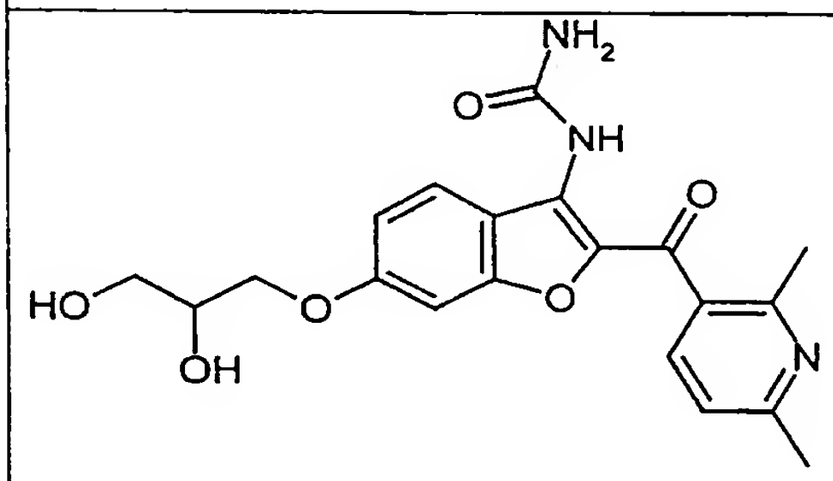
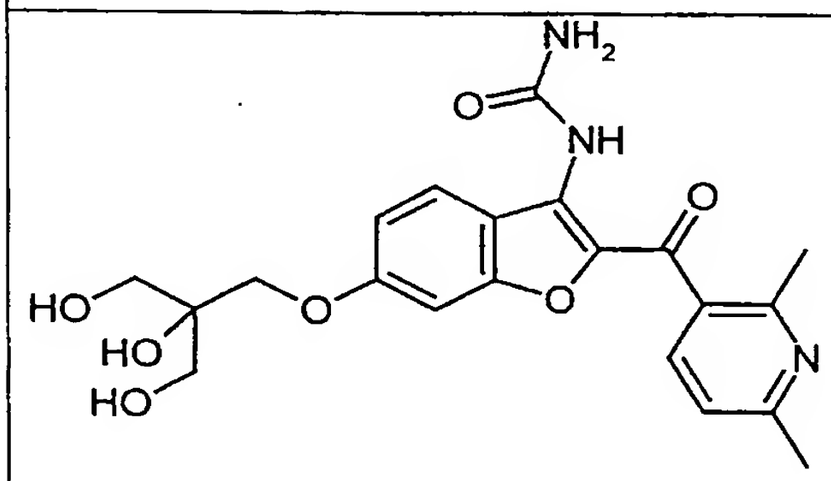
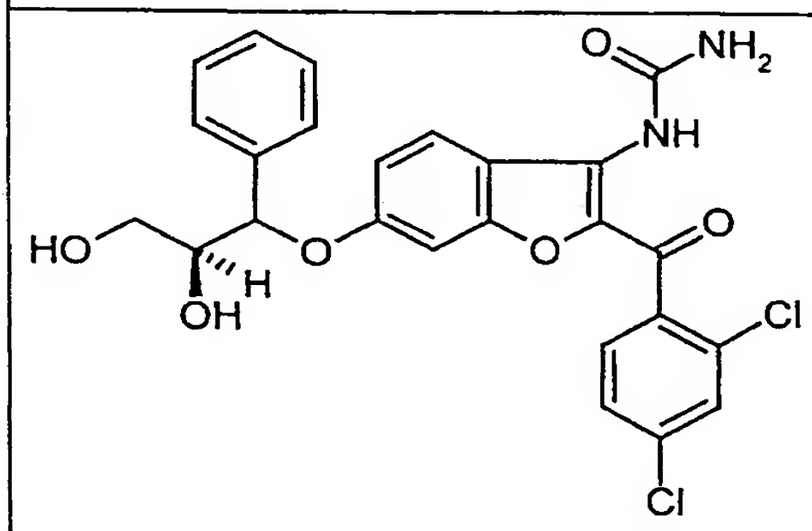

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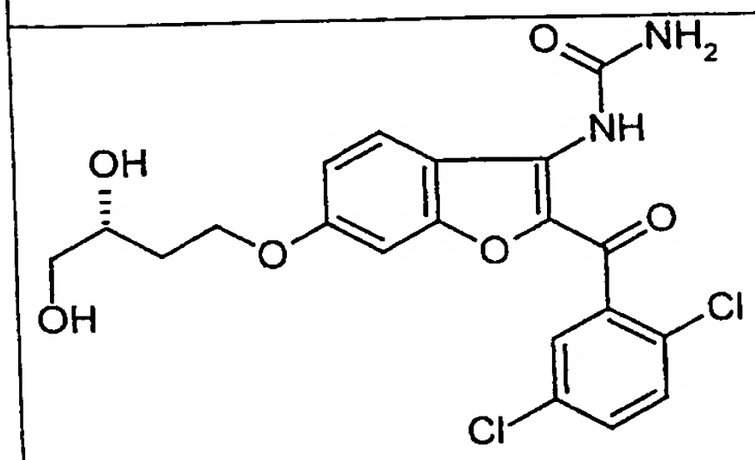
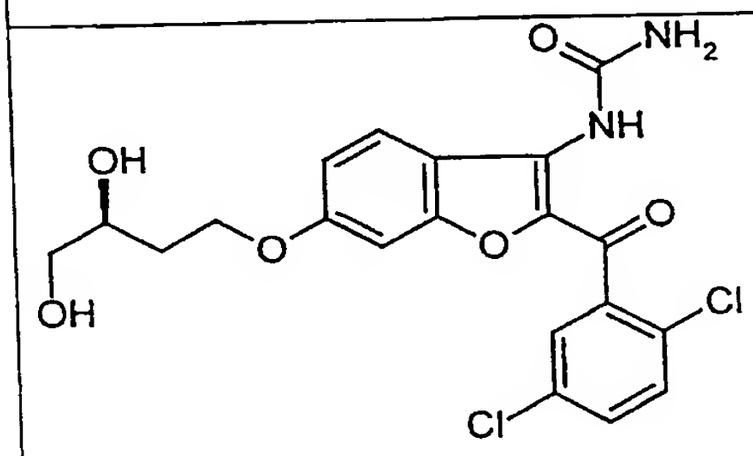
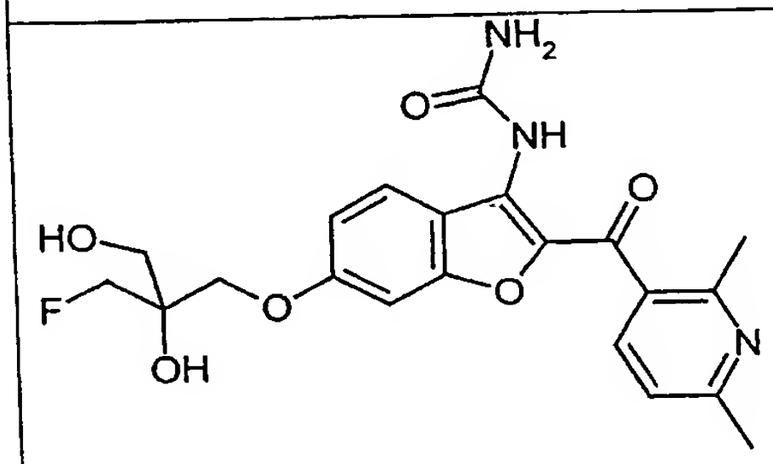
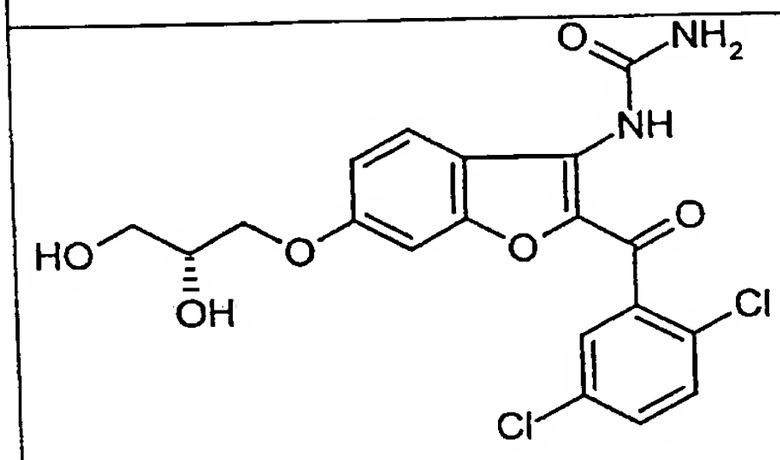
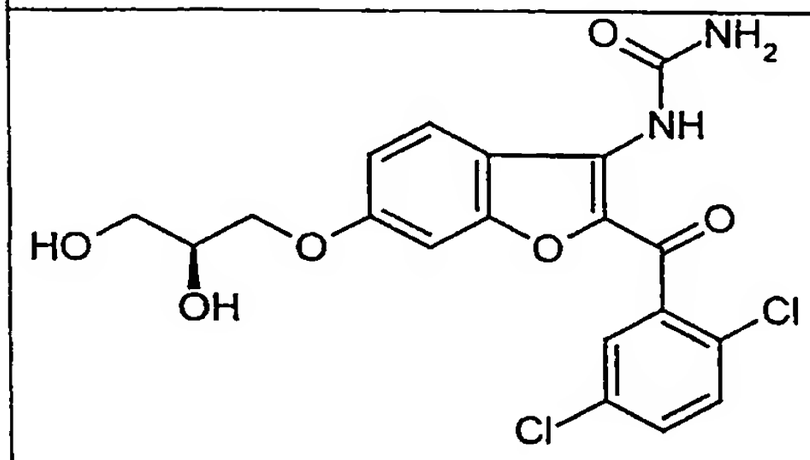
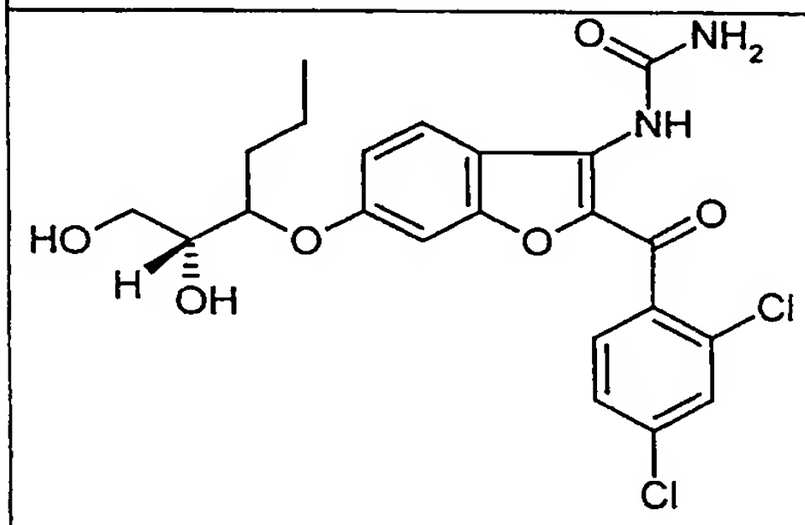
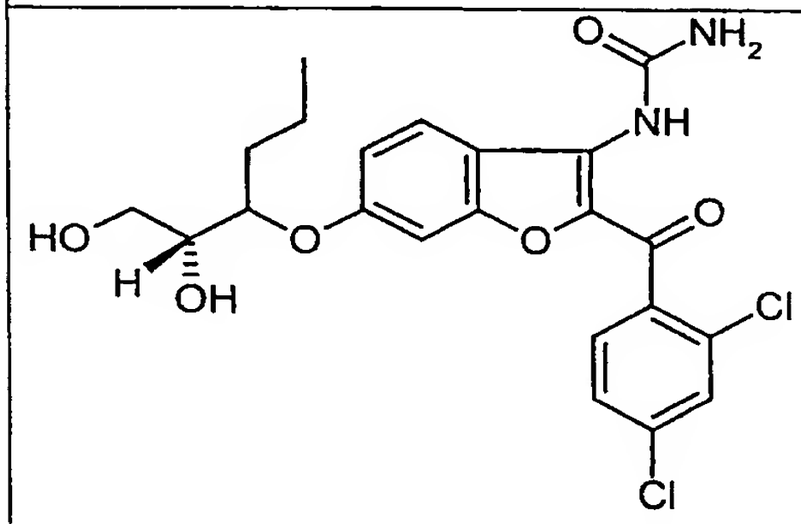
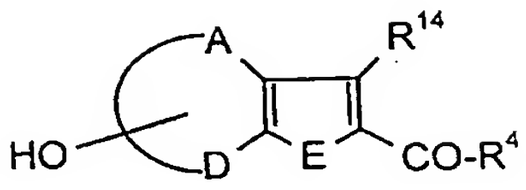



 R-ENANTIOMER

Structure
 S-ENANTIOMER
 DIASTEREOMER A
 DIASTEREOMER B

A process for the preparation of the compounds of the general formula (I) has additionally been found, characterized in that,

that in the case in which R^5 denotes alkyl substituted by two vicinal hydroxyl-groups

[A] compounds of the general formula (II)



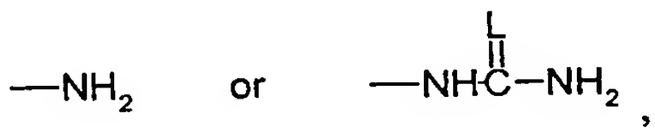
(II)

in which

R^4, A, D and E have the abovementioned meaning,

and

R^{14} denotes a residue of a formula



wherein L has the abovementioned meaning,

first are reacted with compounds of the general formula (III)

$$R^{15}\text{-}CH_2\text{-}Z' \qquad \text{(III)}$$

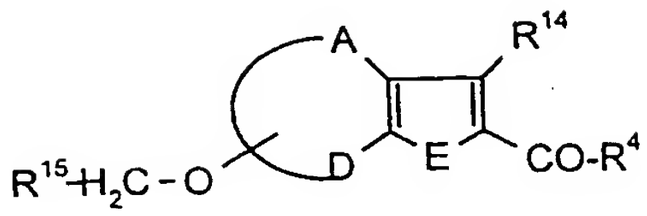
in which

R^{15} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by phenyl or nitro- or halogen-substituted phenyl and/or halogen,

and

Z' denotes a leaving group such as mesyl, tosyl, chlorine, bromine or iodine

in inert solvent and in presence of a base to compounds of the general formula (IV)



(IV)

in which

A, D, E, R^4, R^{14} and R^{15} have the abovementioned meaning,

and in a last step are reacted with osmiumtetroxide (OsO_4) / N-methylmorpholino-N-oxide in inert solvents,

or

in the case in which R^5 denotes alkyl substituted by two to five hydroxyl groups

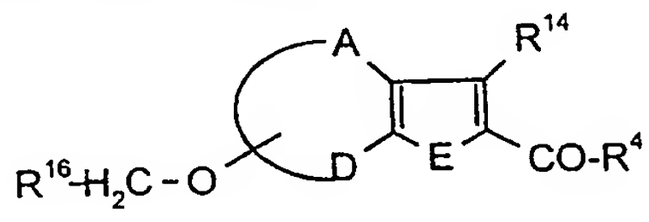
[B] compounds of the general formula (II) are reacted with compounds of the general formula (V)

$$R^{16}\text{-}CH_2OH \qquad (V)$$

in which

R^{16} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by hydroxyl,

in inert solvents and in the presence of triphenylphosphine / diethylazodicarboxylate to compounds of the general formula (VI)



(VI)

in which

A, D, E, R^4, R^{14} and R^{16} have the abovementioned meaning

and in a last step are reacted with OsO_4/N-methylmorpholino-N-oxide inert solvents,

or

[C] compounds of the general formula (II) are reacted with alcohols of the general formula (VII)

$$R^5\text{-}OH \qquad (VII)$$

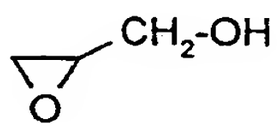
in which

R^5 has the abovementioned meaning

in inert solvents and in presence of triphenylphosphine / diethylazodicarboxylate

or

[D] compounds of the general formula (II) are reacted with the compound of the formula (VIII)



(VIII)

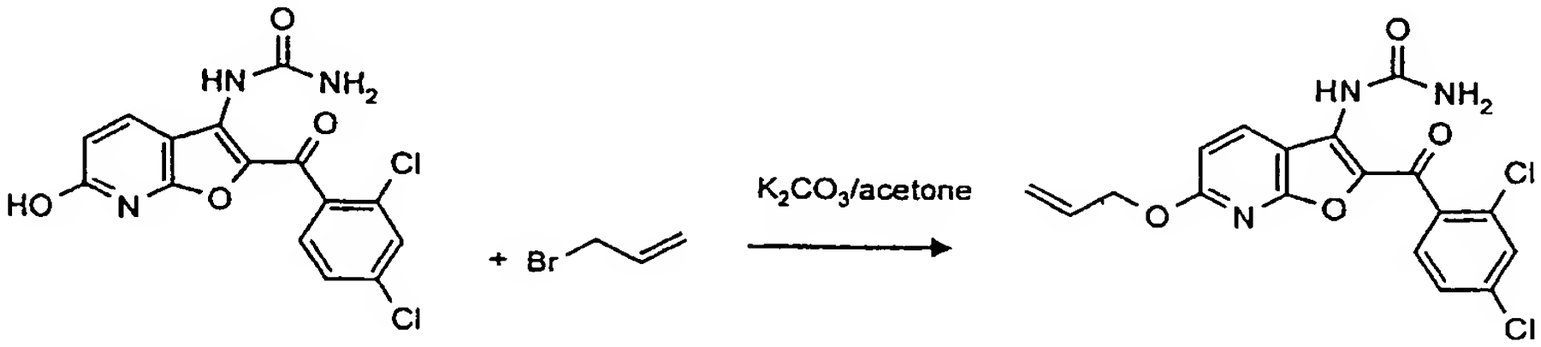
in inert solvents and in the presence of a base and titanium-(IV)isopropylate

and in the case

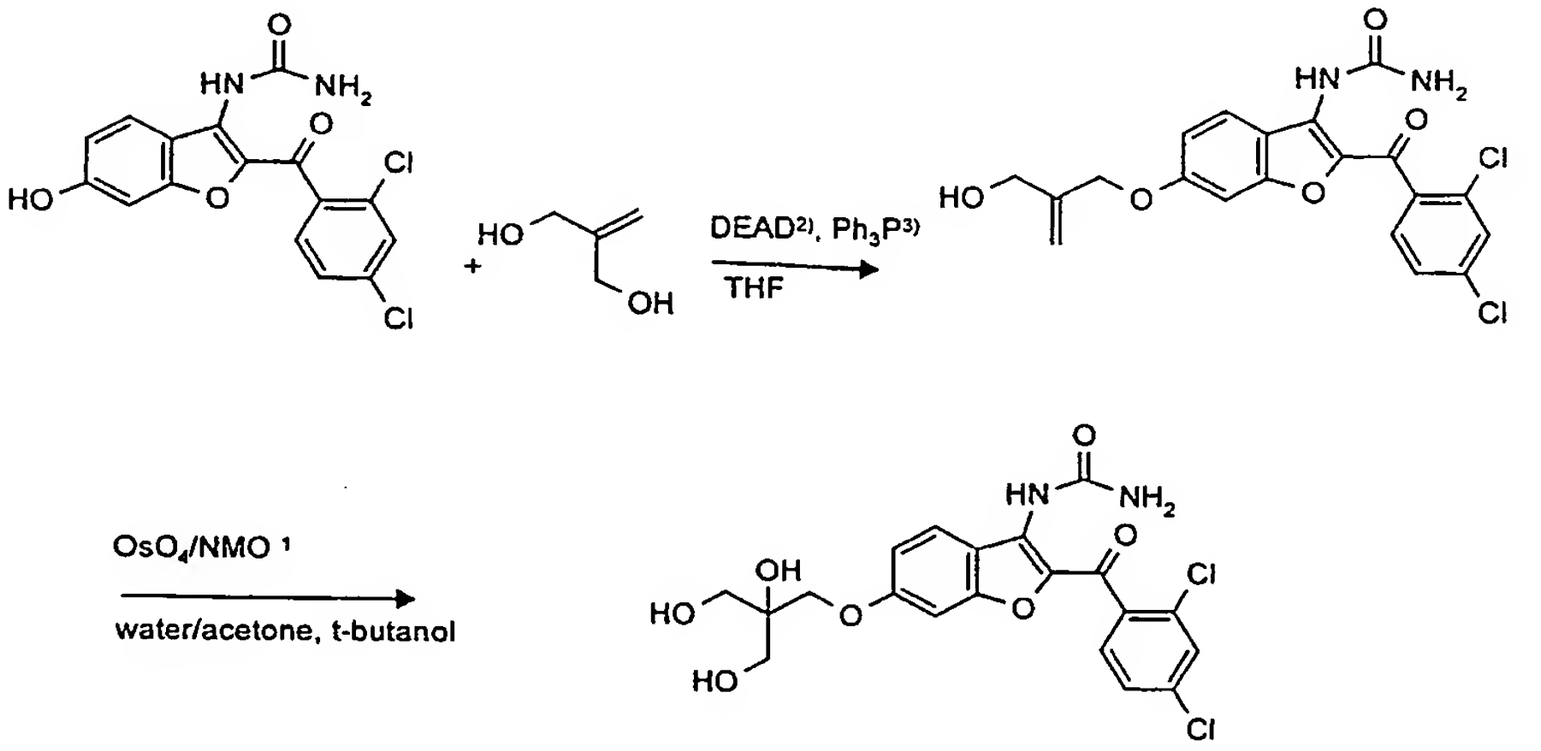
in which R^1, R^2 and/or $R^3 \neq H$ the free amino groups are derivated optionally by common methods.

The process according to the invention can be illustrated by way of example by the following equations:

[A]

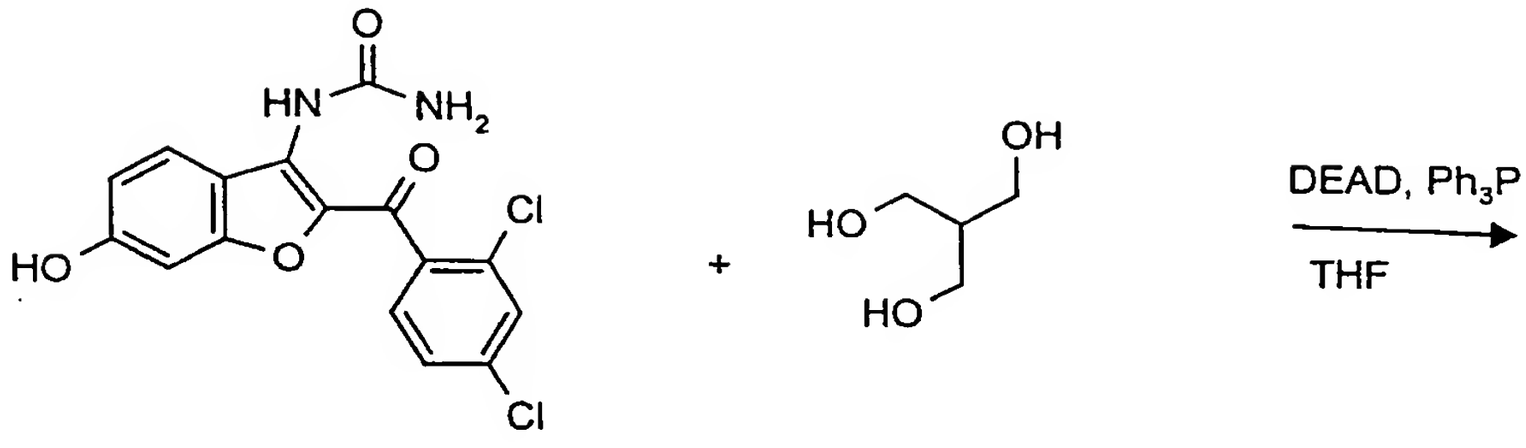


[B]

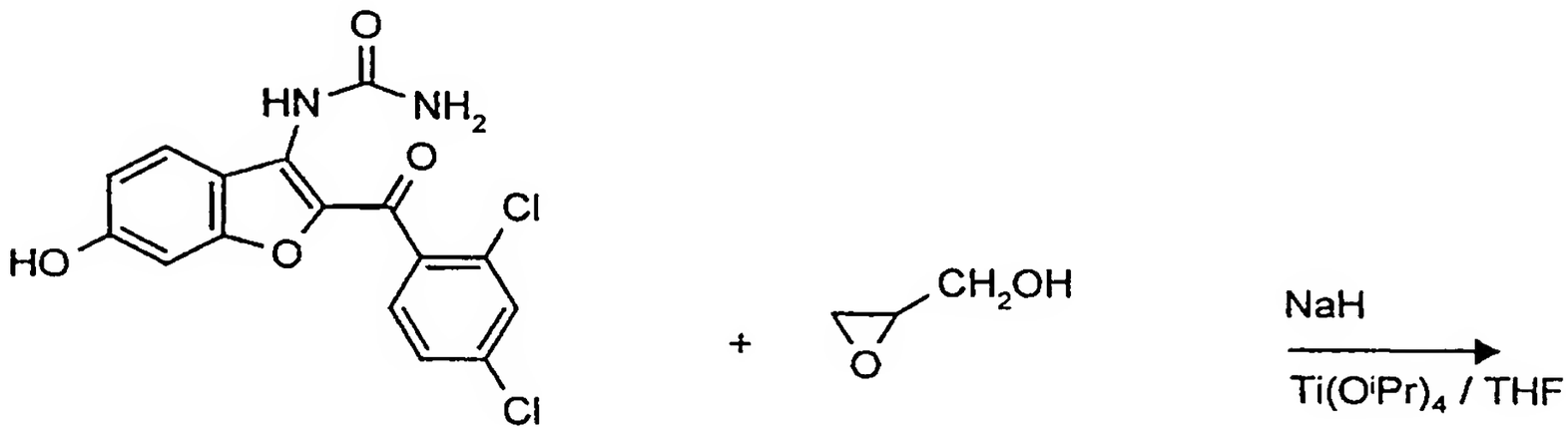


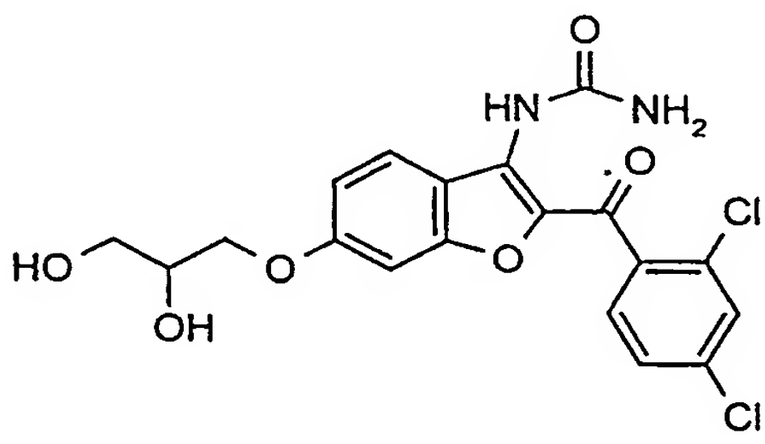
1) N-Methylmorpholino-N-oxide
2) diethylazodicarboxylate
3) triphenylphosphine

[C]



[D]





Suitable solvents for the different processes [A] - [D] are generally water or customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofurane (THF), ethylacetate, acetone, dimethylsulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol, butanol or t-butanol, or halogenohydrocarbons such as dichloromethane, dichloroethane, trichloromethane or tetrachloromethane. Acetone is preferred for the first step of [A] and water/acetone/t-butanol for all processes with OsO_4/N-methyl-morpholino-N-oxide.

Tetrahydrofurane is preferred for the process with the system triphenylphosphine / diethylazodicarboxylate.

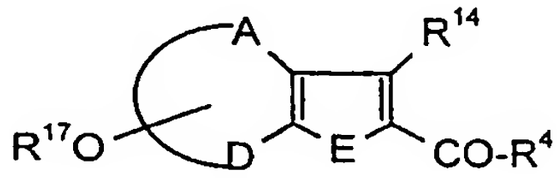
Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or organic amines (trialkyl(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine or methylpiperidine or amide such as sodium amides, lithium butyl amide or butyllithium. It is also possible to employ alkali metals, such as sodium, or their hydrides such as sodium hydride, as bases. Potassium carbonate for the first step of [A] and sodium hydride for process [D] are preferred.

The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formula (II).

The processes are in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

The processes are generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (II) are known or new and can be prepared by cleavage of the protecting group, e.g. by hydrogenation (R^{17} = benzyl) of compounds of the general formula (IX)



(IX)

in which

A, D, E, R^4 and R^{14} have the abovementioned meaning

and

R^{17} denotes a hydroxyl protecting group, preferably methyl or benzyl,

wherein in the case of R^{14} = $-NH_2$ compounds of the general formula (IX) are first reacted with

compounds of the general formula (X)

$$R^{18}\text{-}N{=}C{=}L \quad (X)$$

in which

L has the abovementioned meaning

and

R^{18} has the abovementioned meaning of R^2 and R^3

in inert solvents, if appropriate in the presence of a base,

and in the case of R^2/R^3 = H and L = O,

compounds of the general formula (IX) are first reacted with compounds of the general formula (XI)

$$X\text{-}SO_2\text{-}N{=}C{=}O \qquad (XI)$$

in which

X denotes halogen, preferably chlorine,

and in the case von R^2/R^3 = H and L = S,

compounds of the general formula (IX) are first reacted with NH_4SCN.

The hydroxyl-protective group is in case of R^{17} = benzyl in general removed with hydrogen in ethyl acetate, diethyl ether or tetrahydrofurane. Suitable catalysts are preferably palladium and palladium on charcoal .

Suitable solvents for the steps (IX/X and IX/XI) are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofurane, ethylacetate, dimethylsulfoxide, dimethylformamide or halogenohydrocarbons such as dichloromethane, dichloroethane, trichloromethane or tetrachloromethane. Dichloromethane is preferred.

Suitable bases for these steps are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (tri-alkyl(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabi-cyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine or methylpiperidine or amides such as sodium amids, lithium butyl amide or butyllithium. It is also possible to employ alkali metals, such as sodium, or their hydrides, such as sodium hydride, as bases. Potassium carbonate, triethylamine, sodium hydrogen-carbonate and sodium hydroxide are preferred.

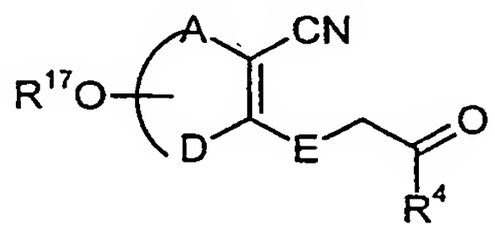
The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formula (IX).

The process is in general carried out in a temperature range from -30°C to +100°C, preferably from –10°C to +50°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (IX) are as species new and are prepared char-acterized in that,

first compounds of the general formula (XII)



(XII)

in which

A, D, E, R^4 and R^{17} have the abovementioned meaning,

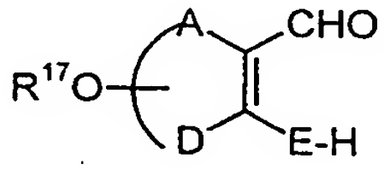
are reacted with a catalytic amount of base such as alkali alcoholates e.g. sodium methanolate, sodium ethanolate or sodium propanolate. Sodium ethanolate ist preferred.

Suitable solvents for the the procedure are generally alcohols such as methanol, ethanol or propanol. Ethanol is preferred.

The process is in general carried out in a temperature range from 0°C to +60°C, preferably from room temperature to 60°C.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (XII) are as species new and can be prepared by reaction of compounds of the general formula (XIII)

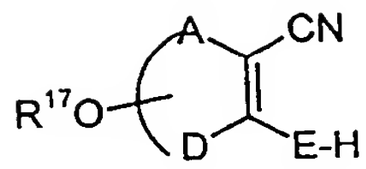


(XIII)

in which

A, D, E and R^{17} have the abovementioned meaning,

with hydroxylamine hydrochloride in the presence of sodium formiate to compounds of the general formula (XIV)



(XIV)

in which

A, D, E and R^{17} have the abovementioned meaning,

and in a next step are reacted with compounds of the general formula (XV)

$$R^4\text{-}CO\text{-}CH_2\text{-}T \quad (XV)$$

in which

R^4 has the abovementioned meaning,

and

T represents halogen, preferably bromine,

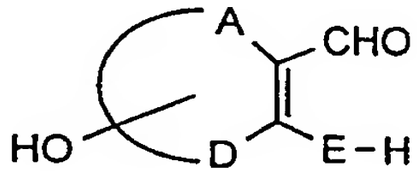
in inert solvents and in the presence of a base.

Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include acetone, ethers such as diethyl ether, dioxane or tetrahydrofurane, aceton, dimethylsulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Acetone and dimethylformamide are preferred.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The compounds of the general formula (IX) in which R^{14} denotes NH_2 can be prepared like described above or in a single step procedure by reacting compounds of the general formula (XIV) with compounds of the general formula (XV) in the presence of a surplus of sodium ethylate under reflux .

The compounds of the general formula (XIII) can be prepared by reaction of compounds of the general formula (XVI)



(XVI)

in which

A, D and E have the abovementioned meaning

with hydroxyl protecting agents of the general formula (XVII)

$$R^{17}\text{-}Z' \qquad \text{(XVII)}$$

in which

R^{17} has the abovementioned meaning

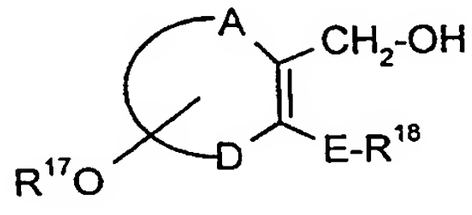
and

Z' denotes a leaving group such as halogen, preferably chlorine, bromine, mesyl or tosyl,

in inert solvents, preferably acetone or dimethylformamide,

and in case A and D form a heterocycle,

by reaction of compounds of the general formula (XVIII)



(XVIII)

in which

A, D, E and R^{17} have the abovementioned meaning,

and

R^{18} denotes methyl,

with MnO_2, followed by BCl_3 / CH_2Cl_2.

The compounds of the general formulae (III), (V), (VII), (VIII), (X), (XI), (XV) and (XVIII) are known and in some cases new and can be prepared by customary methods.

The compounds of the general formulae (II), (IV), (VI), (IX), (XII), (XIII), (XIV), (XVII) and (XVIII) are new or can be prepared like described above.

Surprisingly it was found that compounds given by the general formula (I) inhibited oxygen radical formation as well as TNFα (tumor necrosis factor) production. These compounds elevated cellular cyclic AMP by inhibition of phagocyte phosphodiesterase (PDE) activity.

The compounds according to the invention specifically inhibit the production of superoxide by polymorphonuclear leukocytes (PMN). Furthermore, these compounds inhibit TNFα release in human monocytes in response to a variety of stimuli including bacterial lipopolysaccharide (LPS), complement-opsonized zymosan (ZymC3b) and IL-1ß.

The described effects are probably mediated by the elevation of cellular cAMP due to inhibition of the type IV phosphodiesterase responsible for its degradation.

They can therefore be employed in medicaments for the treatment and prevention of acute and chronic inflammatory processes.

The compounds according to the invention are preferably suitable for the treatment and prevention of acute and chronic inflammation and auto immune diseases, such as emphysema, alveolitis, shock lung, all kind of COPD, ARDS, asthma and bronchitis, cystic fibrosis, eosinophilic granuloma, arteriosclerosis, arthrosis, inflammations of the gastro-intestinal tract, myocarditis, bone resorption diseases, reperfusion injury, Crohn's disease, ulcerative colitis, system lupus erythematosus, type I diabetes mellitus, psoriasis, anaphylactoid purpura nephritis, chronic glomerulonephtritis, inflammatory bowel disease, other benign and malignant proliferative skin diseases, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, sepsis and septic shock, toxic shock syndrome, grafts vs host reaction, allograft rejection, treatment of cytokine mediated chronic tissue degeneration, rheumatoid arthritis, arthritis, rheumatoid spondylitis and osteoarthritis and coronary insufficiency, myalgias, multiple sclerosis, malaria, AIDS, cachexia, prevention of tumor growth and invasion of tissue, leukemia, depression, memory impairment and acute stroke. The compounds according to the invention are additionally suitable for reducing the damage to infarct tissue after reoxygenation. In this case the simultaneous administration of allopurinol to inhibit xanthine oxidase is of advantage. Combination therapy with superoxide dismutase is also of use.

Test description

1. Preparation of human PMN

Blood was taken from healthy subjects by venous puncture and neutrophils were purified by dextran sedimentation and resuspended in the buffered medium.

2. Inhibition of FMLP-stimulated production of superoxide racidal anions.

Neutrophils (2.5×10^5 ml^{-1}) were mixed with cytochrome C (1.2 mg/ml) in the wells of a microtitre plate. Compounds according to the invention were added in dimethyl sulphoxide (DMSO). Compound concentration ranged from 2.5 nM to 10 μM, the DMSO concentration was 0.1% v/v in all wells. After addition of cytochalasin b (5 μg x ml^{-1}) the plate was incubated for 5 min at 37°C. Neutrophils were then stimulated by addition of 4×10^{-8} M FMLP and superoxide generation measured as superoxide dismutase inhibitable reduction of cytochrome C by monitoring the OD_{550} in a microtitre plate spectrophotometer, e.g. a Thermomax microtitre plate spectrophotometer, Initial rates were calculated using a kinetic calculation programme such as a softmax programme. Blank wells contained 200 units of superoxide dismutase.

The inhibition of superoxide production was calculated as follows:

$$\frac{[1-((Rx-Rb))]}{((Ro-Rb))} \cdot 100 = \% \text{ inhibition}$$

Rx = Rate of the well containing the compound according to the invention.

Ro = Rate in the control well.

Rb = Rate in the superoxide dismutase containing blank well.

Compounds according to the invention have IC_{50} values in the range 0.001μM-1 μM (see Table B).

3. Measurement of PMN cyclic AMP concentration

The compounds according to the invention were incubated with 3.7 x 10^6 PMN for 5 min at 37°C before addition of 4 x 10^{-8} M FMLP. After 6 min protein was precipitated by the addition of 1% v/v conc. HCl in 96% v/v ethanol containing 0.1 mM EDTA. After centrifugation the ethanolic extracts were evaporated to dryness under N_2 and resuspended in 50 mM Tris/HCl pH 7.4 containing 4 mM EDTA. The cyclic AMP concentration in the extracts was determined using a cyclic AMP binding protein assay supplied by Amersham International plc. Cyclic AMP concentrations were expressed as percentage of vehicle containing control incubations.

Compounds elavate the cAMP-level at 1 µM compound 0-400% of control values.

4. Assay of PMN phosphodiesterase

This was performed as a particulate fraction from human PMN essentially as described by Souness and Scott (Biochem. J. 291, 389-395, 1993). Particulate fractions were treated with sodium vanadate / glutathione as described by the authors to express the discrete stereospecific site on the phosphodiesterase enzyme. Compounds according to the invention had IC_{50} values ranging from 0,001 µM to 1 µM (see Table B).

5. Assay of human platelet phosphodiesterase

This was performed essentially as described by Schmidt et al. (Biochem. Pharmacol. 42, 153-162, 1991) except that the homogenate was treated with vanadate glutathione as above. Compounds according to the invention had IC_{50} values greater than 100 µM.

6. Assay of binding to the rolipram binding site in rat brain membranes

This was performed essentially as described by Schneider et al. (Eur. J. Pharmacol. 127, 105-115, 1986). Compounds according to the invention had IC_{50} values in the range 0.01 to 10 µM.

7. Preparation of human monocytes

Blood was taken from normal donors. Monocytes were isolated from peripheral blood by density centrifugation, followed by centrifugal elutriation.

8. Endotoxin induced TNF release

Monocytes (1×10^6 ml^{-1}) were stimulated with LPS (2 µg ml^{-1}) and coincubated with the compounds at different concentrations (10^{-4} to 10 µg ml^{-1}). Compounds were dissolved in DMSO/medium (2% v/v). The cells were incubated in RPMI-1640 medium glutamine/FCS supplemented and at 3°C in a humidified atmosphere with 5% CO_2. After 18 to 24 hours TNF was determined in the supernatants by an human TNF specific ELISA (medgenix). Controls were non-stimulated and LPS stimulated monocytes without compounds.

9. Endotoxin induced shock lethality in mice

B6D2F1 mice (n=10) were sensitized with galactosamine (600 mg/kg), and shock and lethality were triggered by LPS (0.01 µg/mouse). The compounds were administered intravenously 1 hour prior LPS. Controls were LPS challenged mice without compound. Mice were dying 8 to 24 hours post LPS challenge.

The galactosamine / LPS mediated mortality was reduced.

10. Stimulation of human monocytes and determination of cytokine levels

Human monocytes ($2x10^5$ in 1 ml) were stimulated with 100 ng/ml LPS, 0.8 mg/ml zymC3b or 10 ng/ml IL-1ß in the presence of test compounds. The final DMSO concentration was maintained at 0.1 % v/v. Cells were incubated overnight in a humidified atmosphere of 5% CO_2 at 37°C. Supernatants were

harvested and stored at –70°C. The TNFα concentration was measured by ELISA using the A6 anti-TNF monoclonal antibody (Miles) as the primary antibody. The secondary antibody was the polyclonal anti-TNFα antibody IP300 (Genzyme) and the detection antibody was a polyclonal anti-rabbit IgG alkaline phosphatase conjugate (Sigma). IL-10 was determined by ELISA (Biosource).

Table B

Ex.-No.	$IC_{50}O_2^-$ [μM]	IC_{50}PDE IV [μM]
1	0.008	0.006
6	0.07	0.05
8	0.01	0.015
11	0.008	0.01
24	0.025	0.04
33	0.03	0.016
40	0.03	0.009
43	0.047	0.042

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent, organic solvents can be used as auxiliary solvents if appropriate.

Administration is carried out in a customary manner, preferably orally or parenterally.

In the case of parenteral administration, solutions of the active compound can be employed using suitable liquid vehicles.

In general, it has proved advantageous on intravenous administration to administer amounts from about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg of body weight to achieve effective results, and on oral administration the dosage is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

In spite of this, it may be necessary to depart from the amounts mentioned, in particular depending on the body weight or the type of application route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of relatively large amounts, it is advisable to divide these into several individual doses over the course of the day.

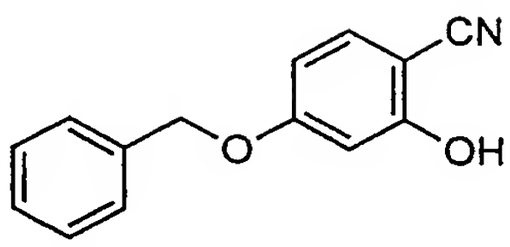
<u>Solvents for thin layer chromatography:</u>

a)	Dichloromethane/methanol	15:1
b)	" "	20:1
c)	" "	50:1
d)	Ethyl acetate	
e)	Cyclohexane/acetone	2:1
f)	Toluene/Ethyl acetate	1:1
g)	Dichloromethane/methanol	40:1
h)	Choroform/methanol/water/acetic acid	70:30:5:5
i)	Dichloromethane/methanol	10:1

Starting compounds

Example I

4-Benzyloxy-2-hydroxy-benzonitrile

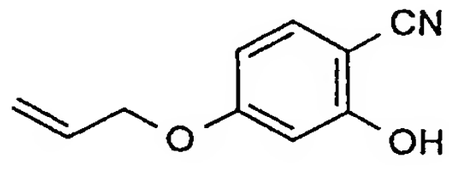


34 g (0.15 mol) 4-benzyloxy-2-hydroxy-benzaldehyde, 12 g (0.17 mol) hydroxylamine hydrochloride and 19 g (0.29 mol) sodium formiate in 170 ml formic acid were stirred at 50°C for 19 h. After cooling the mixture was poured on 200 ml ice/water. Extraction with CH_2Cl_2, evaporation of the solvent and chromatography on silica gel with toluene/ethyl acetate yielded 12 g (35%) of the title compound.

m.p.: 135-136°C

Example II

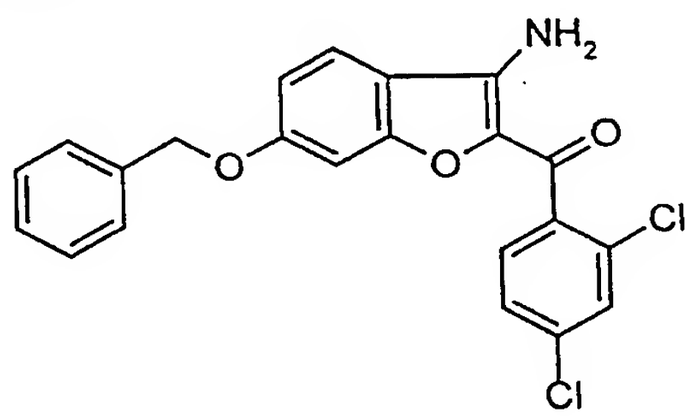
4-Allyloxy-2-hydroxy-benzonitril



Example II was prepared from 4-allyloxy-2-hydroxy-benzaldehyde in analogy to example I.

Example III

3-Amino-6-benzyloxy-2-(2,4-dichlorbenzoyl)-benzofuran



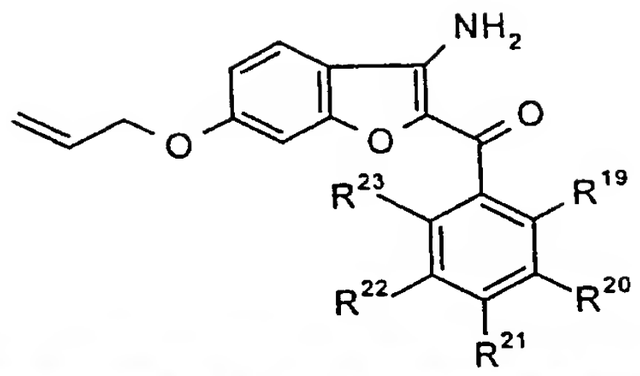
10 g compound of example I (44 mmol) and 5.98 g sodium ethylate (88 mmol) were refluxed in 180 ml ethanol. 30.8 g ω-bromo-2,4-dichloroacetophenone (96 mmol) were added dropwise over a period of 1 hour to the refluxing reaction mixture. After 7 hours the mixture was cooled to room temperature, the solvent was distilled off and the residue further purified by chromatography (CH_2Cl_2, Silicagel 60).

Yield: 11.6 g (63%)

Mp.: 150°C

The following examples were prepared in analogy to example III:

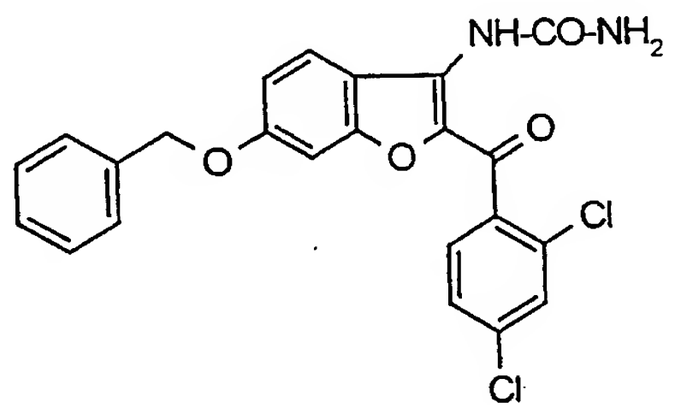
Table I:



Example	$R^{19}/R^{20}/R^{21}/R^{22}/R^{23}$	Mp. (°C)
IV	Cl /H/H/H/Cl	140
V	H/H/Cl/H/H	137
VI	H/Cl/H/H/H	155
VII	Cl/H/H/Cl/H	141
VIII	H/Cl/Cl/H/H	140
IX	Cl/Cl/H/H/H	171

Example X

6-Benzyloxy-2-(2,4-dichlorobenzoyl)-3-ureido-benzofuran



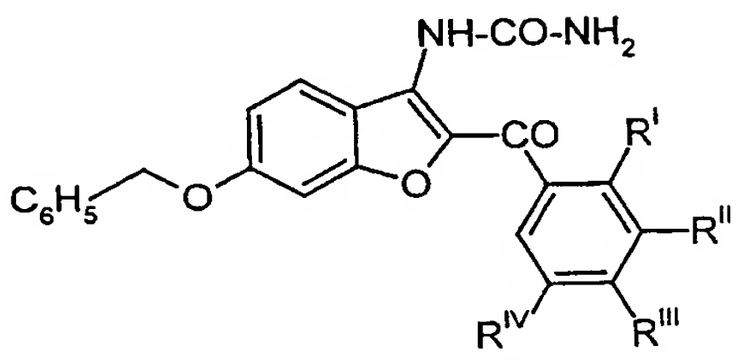
To 12 g (29 mmol) compound of example III in 350 ml dry CH_2Cl_2 2.6 ml (29.8 mmol) chlorosulfonyl isocyanate was added at 0°C. After 1 h at room temperature the mixture was evaporated to dryness. After the addition of 380 ml water, the mixture was stirred for 1.5 h at 60°C. Filtration yielded 12.4 g (95%) of the title compound.

M.p.: 189-191°C

The examples shown in Tables IIa and b are prepared in analogy to the procedure for the compound of example X

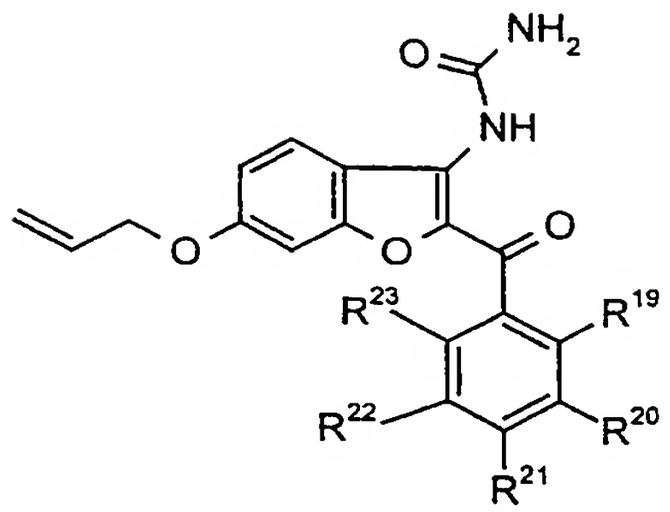
Table IIa

structure



Ex.-No.	R^I	R^{II}	R^{III}	R^{IV}	Yield (% of theory)	R_f*
X a	OCH_3	H	OCH_3	H	69	0.30[b)]
X b	F	H	F	H	82	0.27[g)]
X c	Cl	H	H	H	90	0.18[c)]
X d	H	H	Cl	H	48	0.51[b)]
X e	Cl	H	H	Cl	92	0.47[b)]
X f	CH_3	H	CH_3	H	57	0.45[b)]

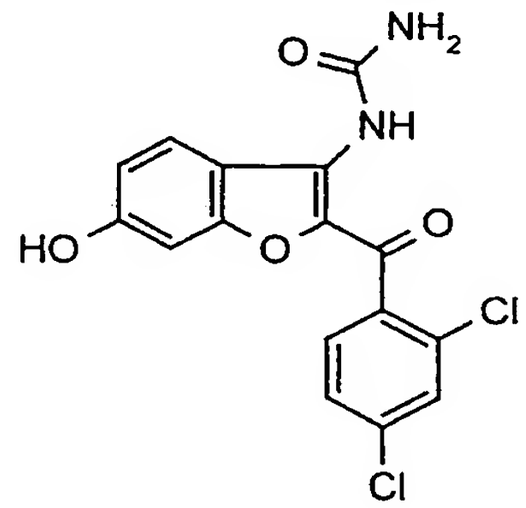
Table II b:



Example	$R^{19}/R^{20}/R^{21}/R^{22}/R^{23}$	Mp. (°C)
X g	Cl/H/Cl/H/H	> 280
X h	H/Cl/H/H/H	180
X i	Cl/H/H/Cl/H	229
X j	Cl/H/H/H/Cl	230
X k	Cl/H/H/H/H	205
X l	Cl/Cl/H/H/H	223
X m	H/Cl/Cl/H/H	214
X n	H/H/Cl/H/H	220

Example XI

2-(2,4-Dichlorobenzoyl)-6-hydroxy-3-ureido-benzofuran

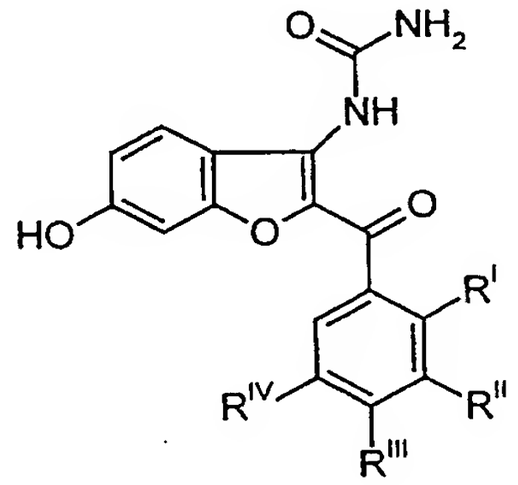


700 mg (1.5 mmol) compound of example X in 15 ml THF were hydrogenated at atmospheric pressure with 10% palladium on charcoal. Filtration over silica gel and evaporation gave the title compound in quantitative yield.

m.p.: 230-231°C

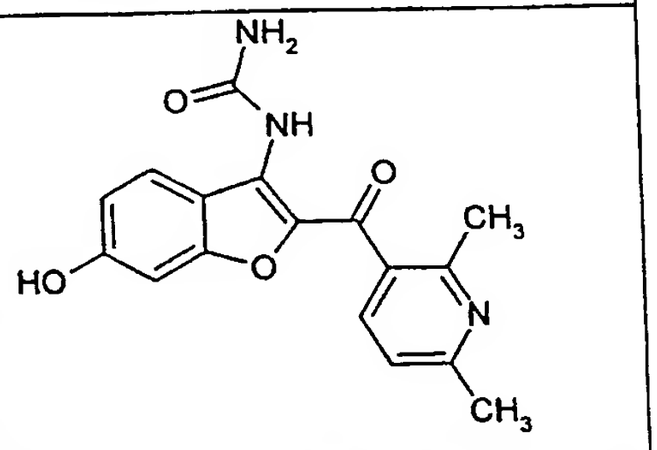
The following examples were prepared in analogy to example XI:

Table IIIa:



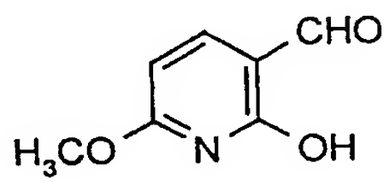
Ex.-No.	R^I	R^{II}	R^{III}	R^{IV}	Yield (% of th.)	R_f *
XI a	F	H	F	H	90	0.76 h)
XI b	H	H	Cl	H	40	0.38 a)
XI c	OCH_3	H	OCH_3	H	88	0.38 a)
XI d	Cl	H	H	H	91	0.36 a)
XI e	Cl	H	H	Cl	91	0.31 b)
XI f	CH_3	H	CH_3	H	58	0.26 b)

Table III b:

Ex.-No.	Structure
XI g	

Example XII

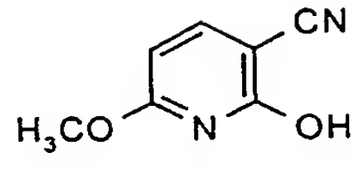
2-Hydroxy-6-methoxy-nicotinaldehyde



8.4 g (0.05 mol) 2,6-dimethoxynicotinaldehyde was dissolved in 75 ml methylene chloride. At 0°C 200 ml (0.2 mol) BCl_3 as 1-molar solution in methylene chloride was added and stirred at room temperature for 20 h. The mixture was poured on ice/water, neutralised and extracted with methylene chloride. Evaporation of the solvent afforded 5.7 g (75%) of the title compound.

Example XIII

2-Hydroxy-6-methoxy-nicotinonitrile



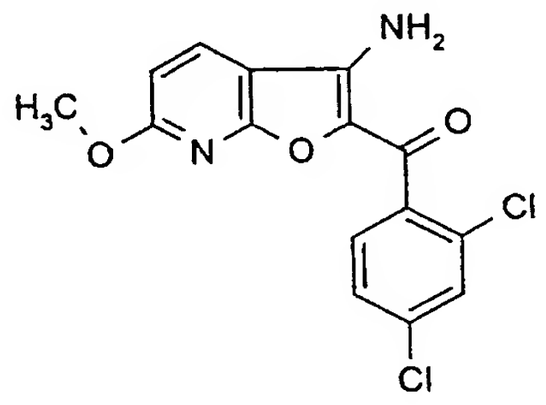
Starting from Example XII, the title compound was prepared in analogy to example I.

Yield: 22%

m.p.: 232°C

Example XIV

3-Amino-6-methoxy-3a,7a-dihydro-furo[2,3-b]pyridin-2-yl)-(2,4-dichlorophenyl)-methanone



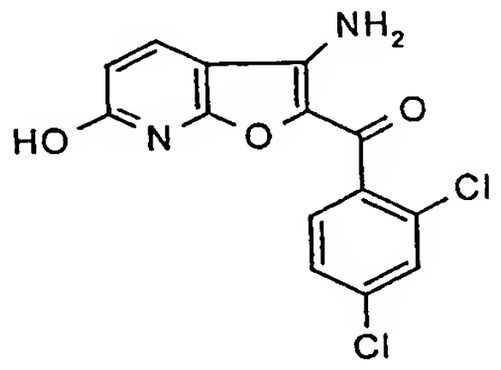
Starting from example XIII, the title compound was prepared in analogy to example III.

Yield: 94%

m.p.: 259-60°C

Example XV

3-Amino-6-hydroxy-3a,7a-dihydro-furo[2,3-b]pyridin-2-yl)-(2,4-dichloro-phenyl)-methanone

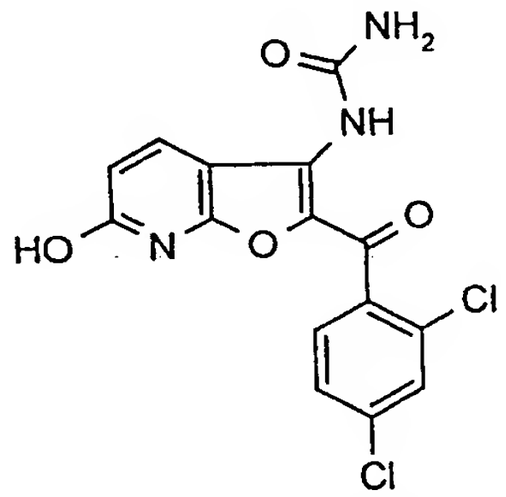


1 g (3 mmol) of the compound of Example XIV was dissolved in 25 ml toluene. 2.8 g (21 mmol) $AlCl_3$ was added in portions at 25°C. The mixture was then stirred under reflux for 1 h. After cooling the mixture was poured on ice. Extraction with ethylacetate, evaporating the solvent and recrystallisation from ethylacetate yielded 0.73 g (75.3%) of the title compound.

m.p.: > 305°C

Example XVI

[2-(2,4-Dichloro-benzoyl)-6-hydroxy-3a,7a-dihydro-furo[2,3-b]pyridin-3-yl]urea



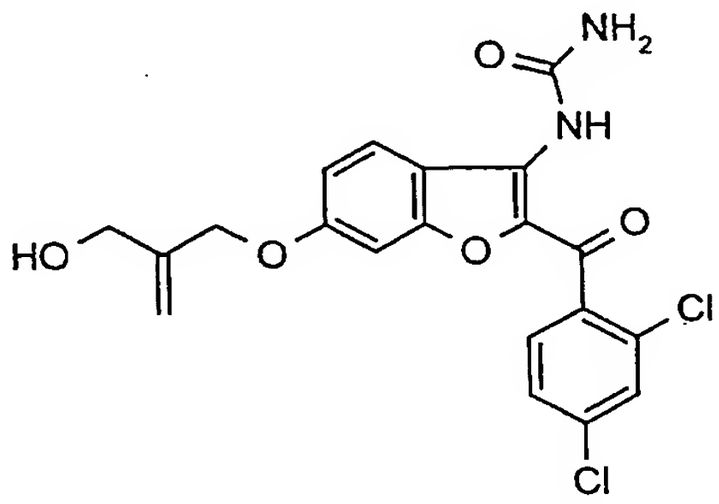
The title compound was prepared in analogy to example X, starting from example XV.

Yield: 86%

R_f: 0.26 (i)

Example XVII

2-(2,4-dichlorobenzoyl)-6-(3-hydroxy-2-methylene-1-propyloxy)-3-ureido-benzofuran

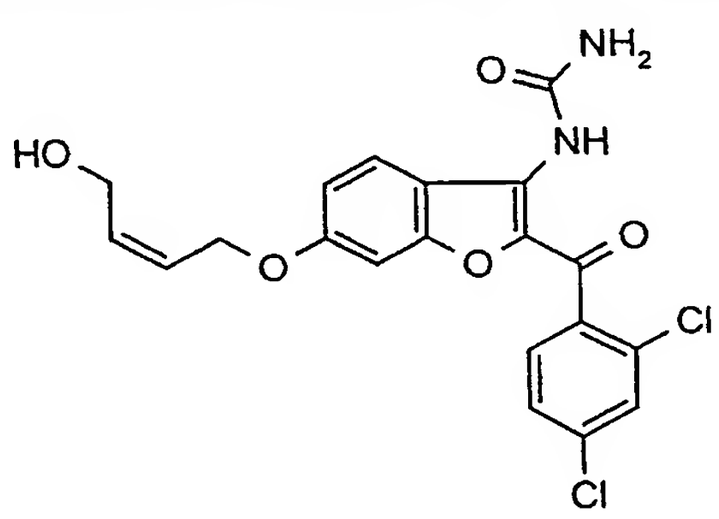


To a solution of 4.5 g (12 mmol) compound of example XI, 1 ml (12 mmol) 2-methylen-1,3-propanediol and 3.2 g (12 mmol) triphenylphosphine in 90 ml dry tetrahydrofuran 2 ml (12 mmol) diethyl azodicarboxylate was added at 0°C. After 4 h at 0°C the solution was diluted with methylene chloride, water was added and the organic layer was separated. Evaporation and chromatography on silica gel with toluene / ethyl acetate yielded 3.5 g (66%) of the title compound.

R_f: 0.61 (d)

Example XVIII

2-(2,4-Dichlorobenzoyl)-6-(4-hydroxy-buty-2-enyl-1-ox)-3-ureido-benzofuran

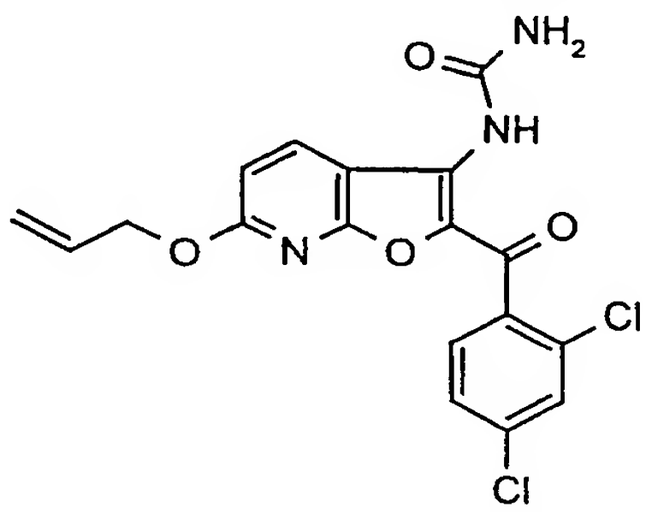


Example XVIII was obtained from example XI in analogy to example XVII.

m.p.: 175-177°C

Example XIX

[6-Allyloxy-2-(2,4-dichloro-benzoyl)-3a,7a-dihydro-furo(2,3-b)pyridin-3-yl]urea

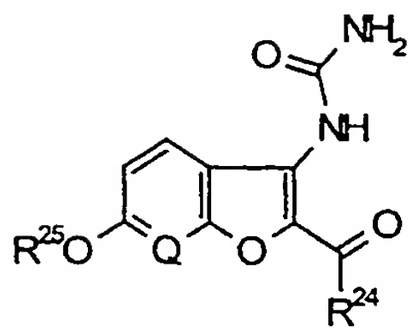


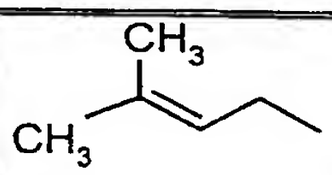
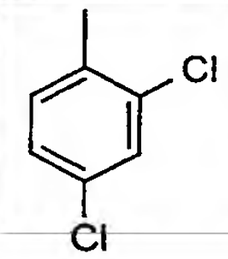
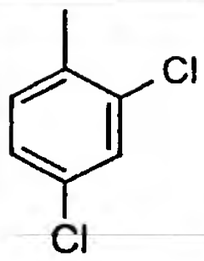
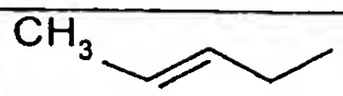
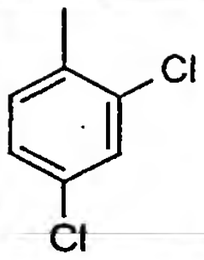
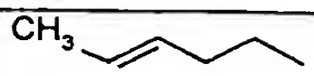
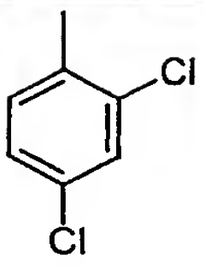
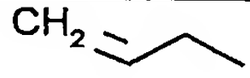
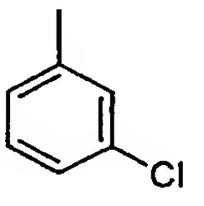
1.1 g (3 mmol) of the compound of Example XVI, 0.42 g (345 mmol) 3-brompropene and 0.41 g (3 mmol) K_2CO_3 were mixed in 30 ml acetone and refluxed for 3 h. After cooling the mixture was poured in 20 ml water. Extraction with ethyl acetate, evaporation of the solvent and recrystallisation from ethanol afforded 0.12 g (9.8%) of the title compound.

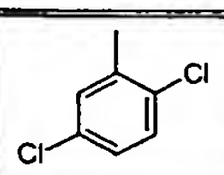
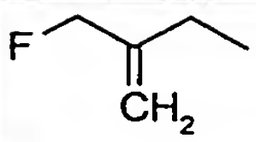
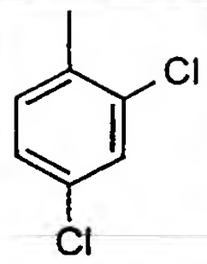
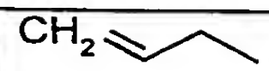
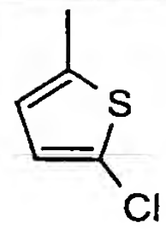
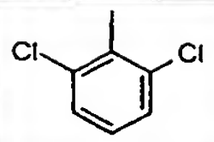
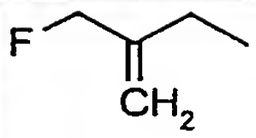
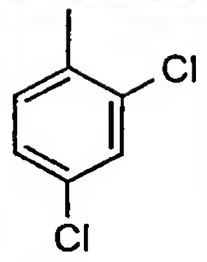
m. p. : 222°C

The compounds in table IV are prepared in analogy to example XIX

Table IV:



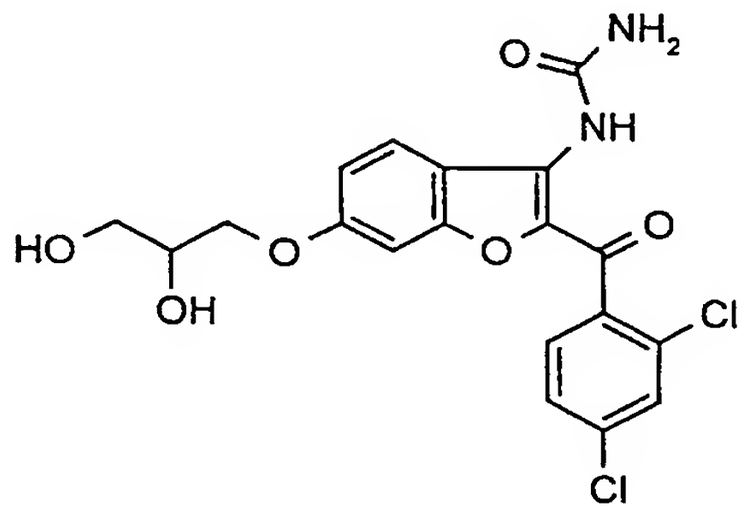
Ex.-No.	R^{25}	Q	R^{24}	Yield (%)	m.p. (°C)
XIX a		CH		93	163-4
XIX b		CH		57	193-4
XIX c		CH		50	175-6
XIX d		CH		71	189-90
XIX e		CH		83	180

Ex.-No.	R^{25}	Q	R^{24}	Yield (%)	m.p. (°C)
XIX f		CH		42	226
XIX g		CH		91	122-4
XIX h		CH		71	214
XIX i		CH		60	230
XIX j		N		45	R_f: 0.45 (i)

Preparation Examples

Example 1

2-(2,4-Dichlorobenzoyl)-6-(2,3-dihydroxy-1-propyloxy)-3-ureido-benzofuran

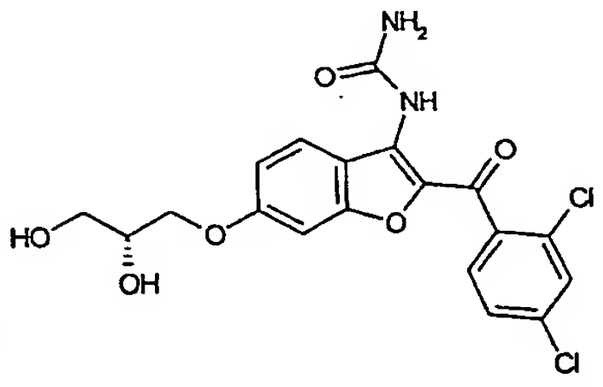
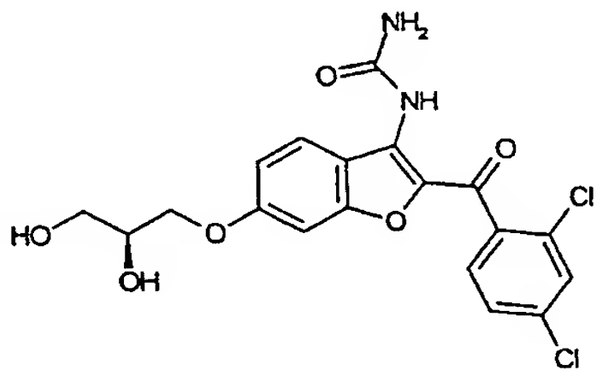
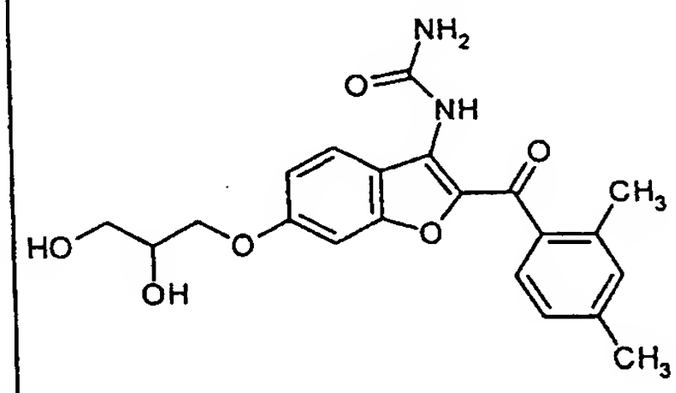
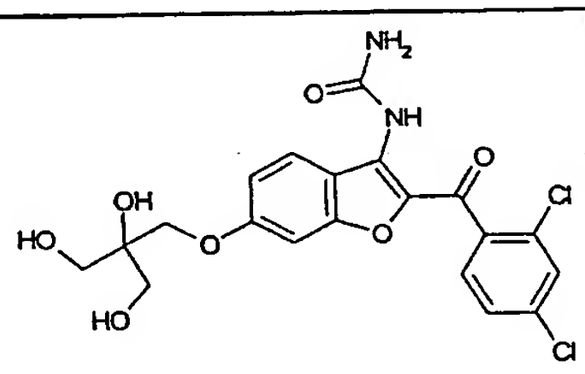


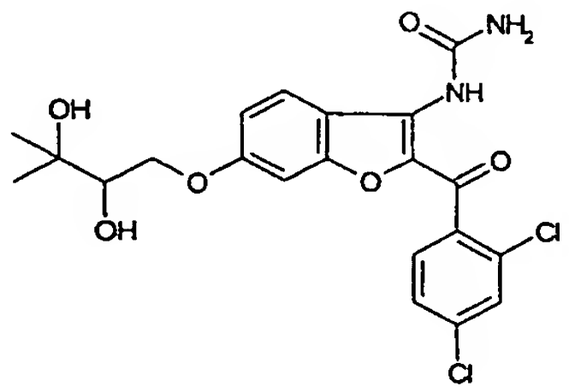
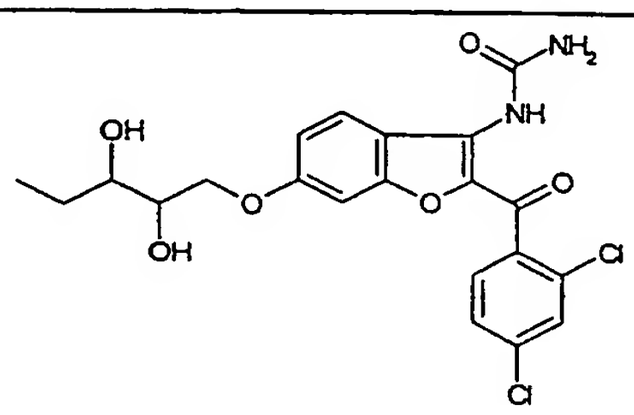
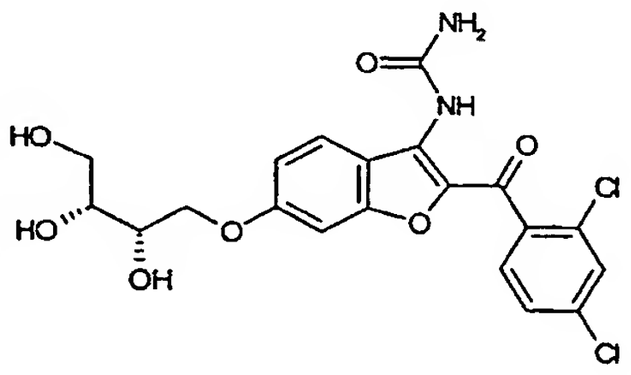
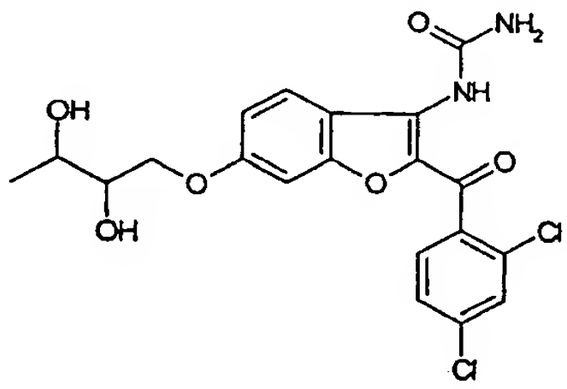
To a solution of 129 mg (1.1 mmol) N-methyl morpholine-N-oxide (NMO) and 0.3 ml osmium tetroxide (2.5% solution in t-butanol) in 5 ml water and 10 ml acetone 405 mg (1 mmol) compound of example X g and 5 ml acetone were added at room temperature. After 47 h additional 129 mg NMO and 0.3 ml osmium tetroxide were added. After another 3 d dichloromethane and 1 N hydrochloric acid was added. The precipitate was separated and triturated with methanol to give 289 mg (66%) of the title compound.

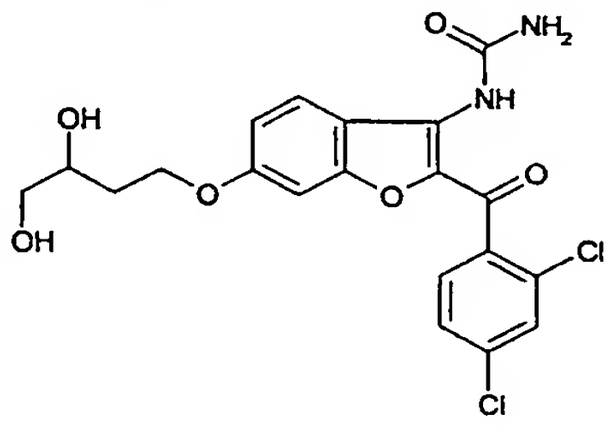
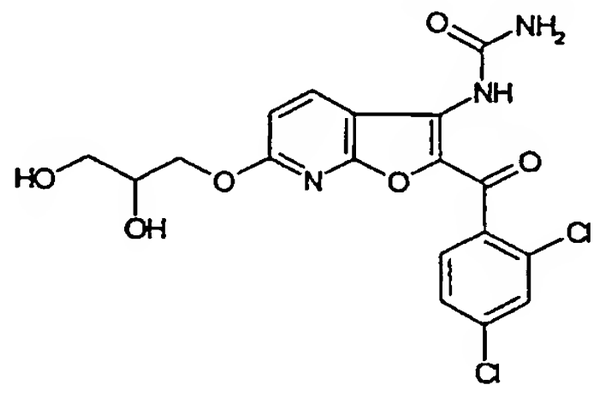
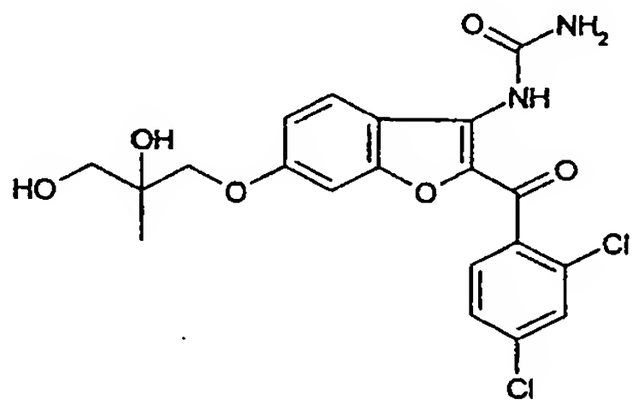
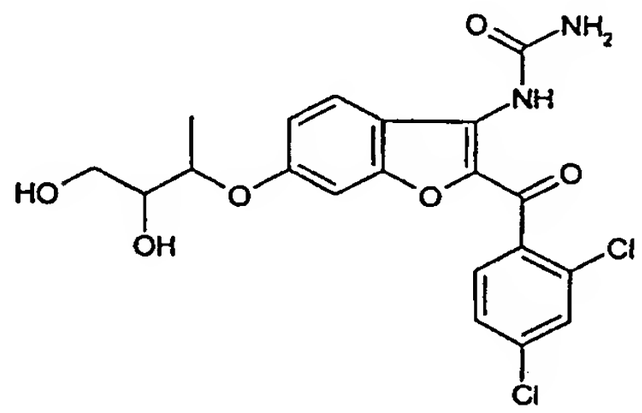
m.p.: 194-195°C

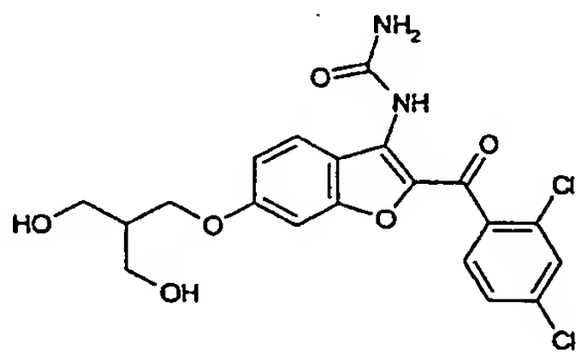
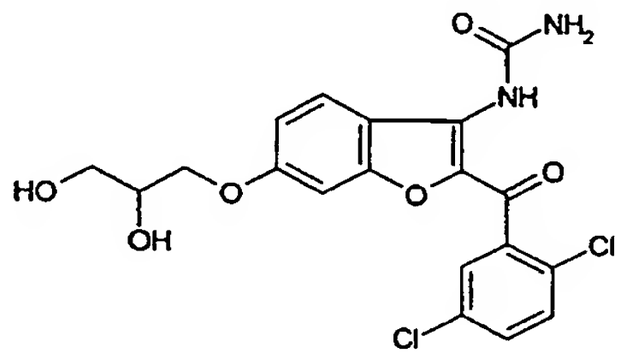
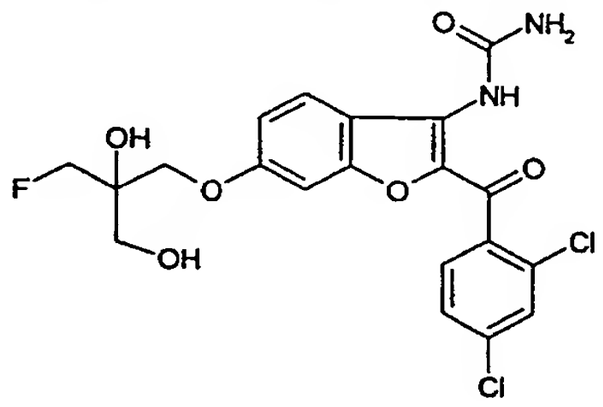
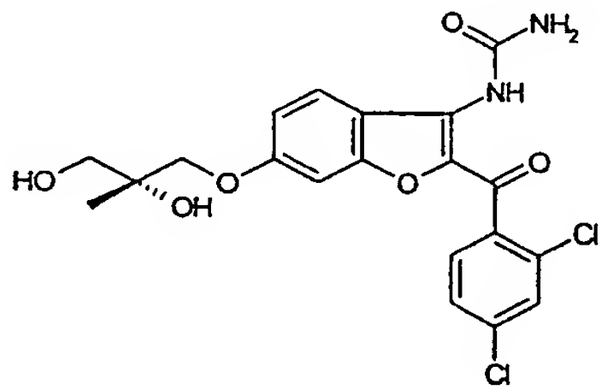
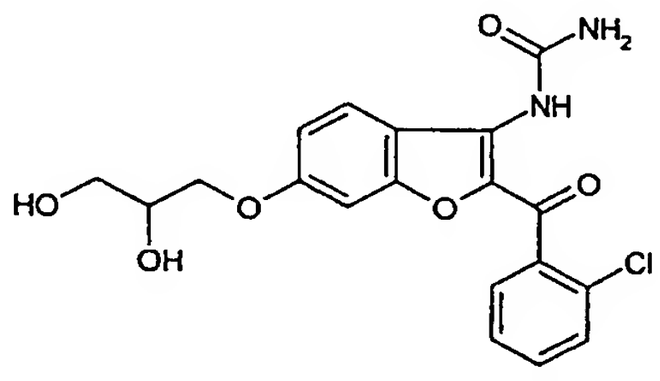
The following examples were prepared in analogy to example 1:

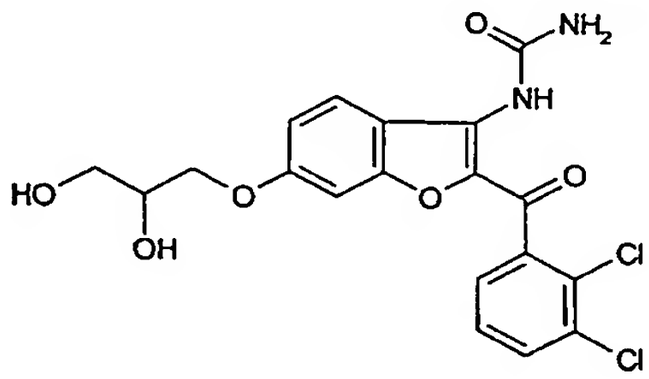
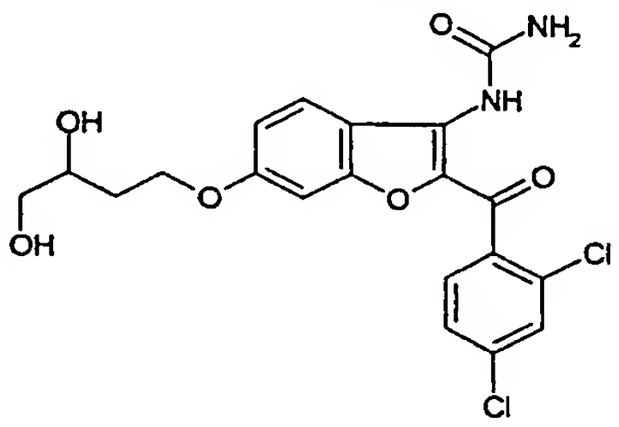
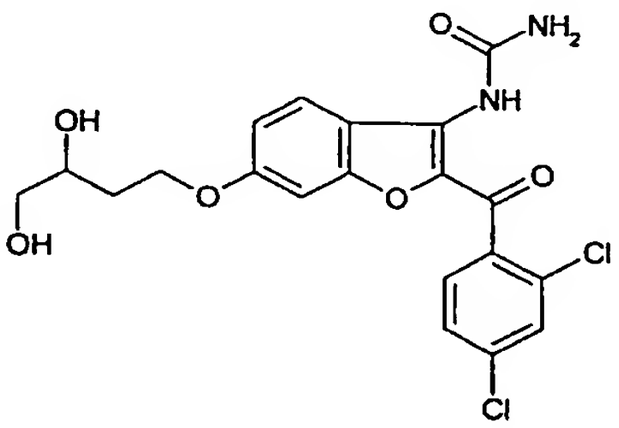
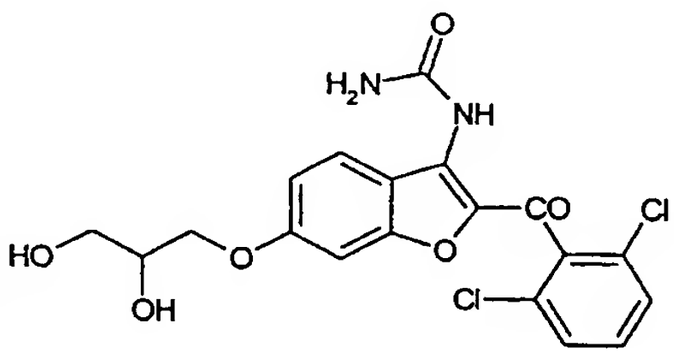
Table V

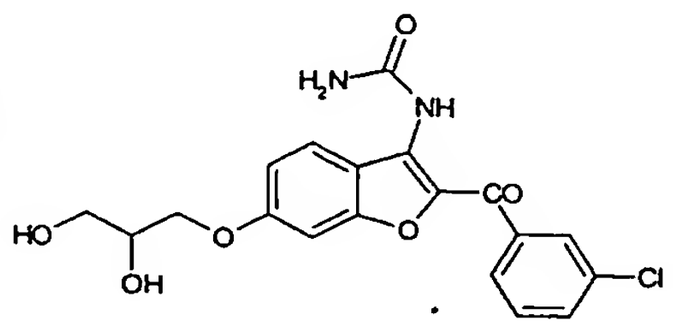
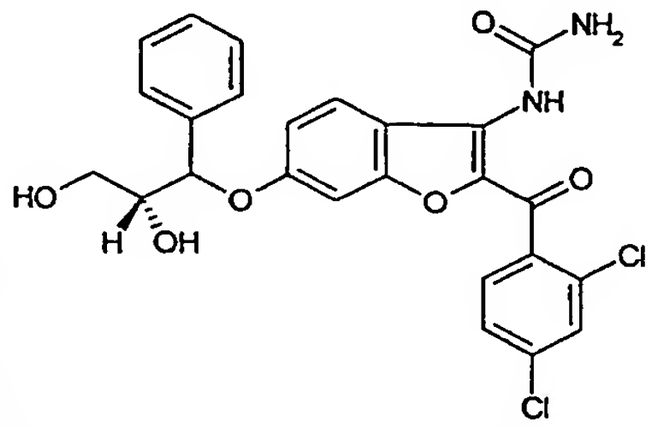
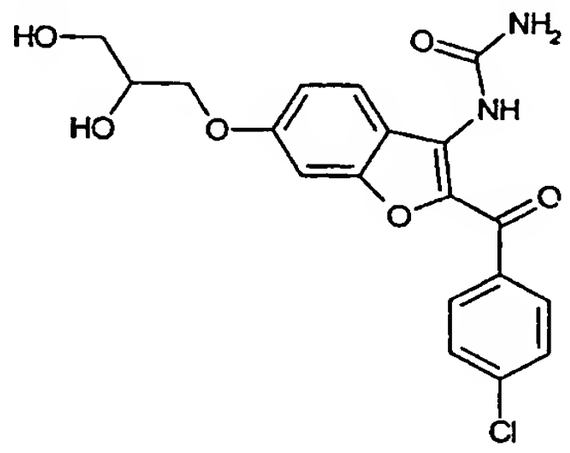
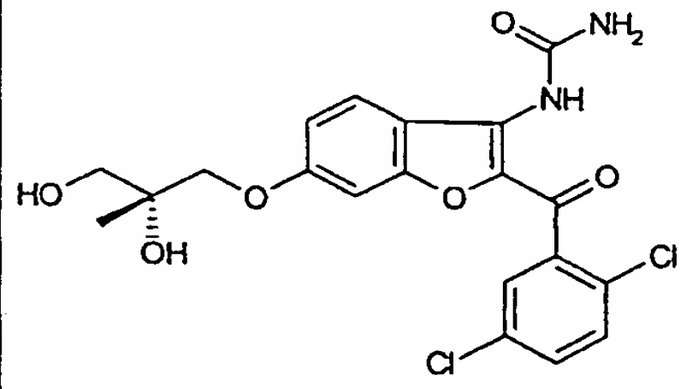
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
2		(R)-ENANTIOMER OF Ex.-No. 1		35	0.30 [d]
3		(S)-ENANTIOMER OF Ex.-No. 1		18	0.30 [d]
4		RACEMATE	191-95		
5			180-85		

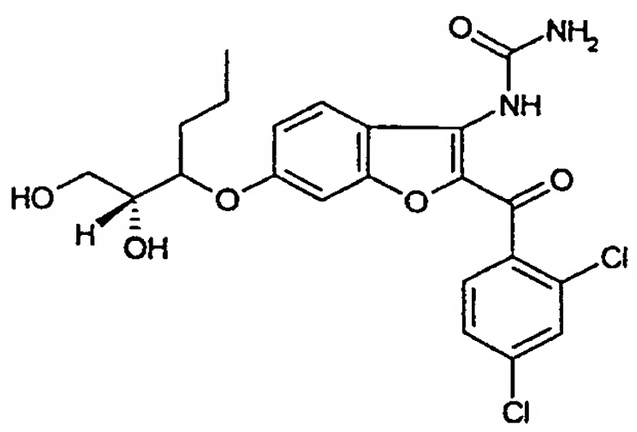
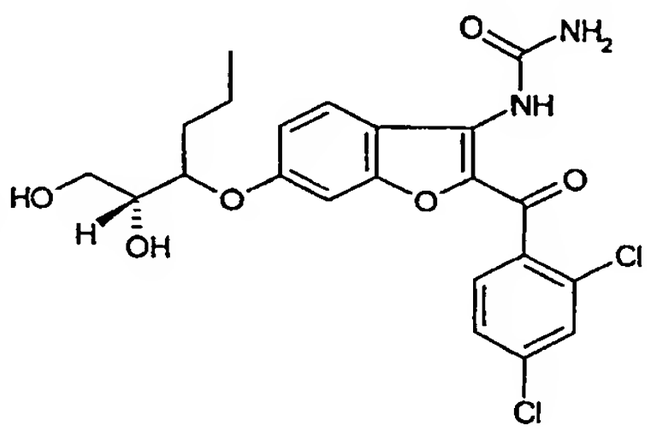
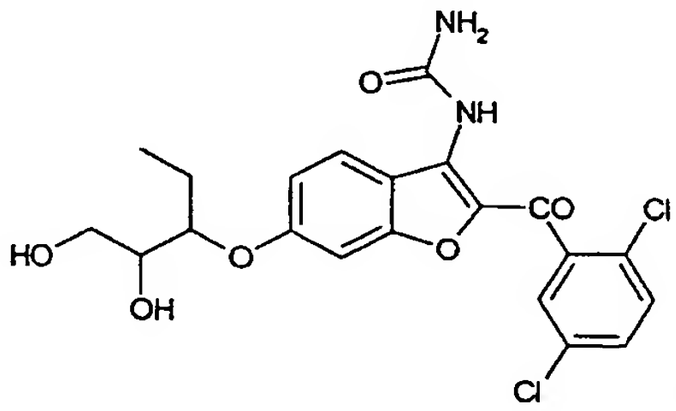
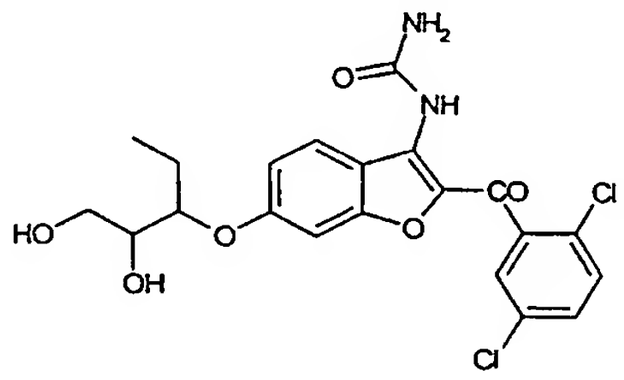
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
6		RACEMATE	157-8	91	
7		MIXTURE OF DIASTEREOMERS	277-8	55	
8		RACEMATE	180-4	91	
9		MIXTURE OF DIASTEREOMERS	201-2	31	

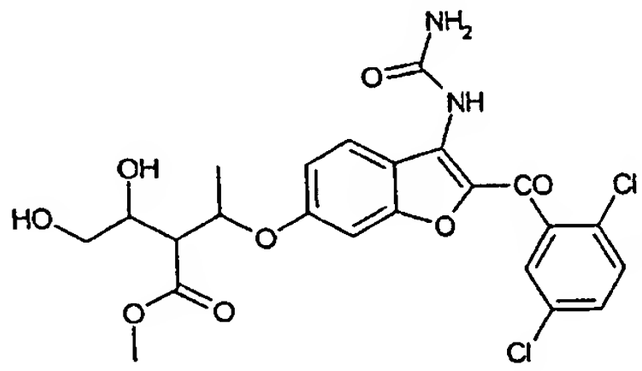
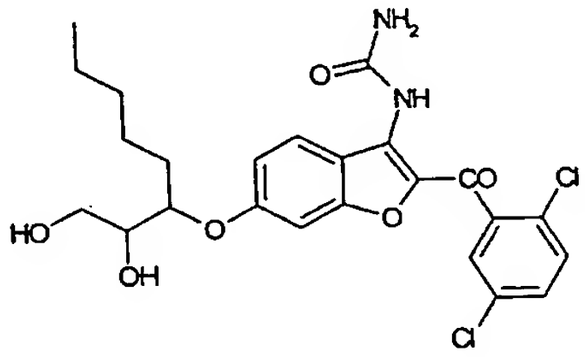
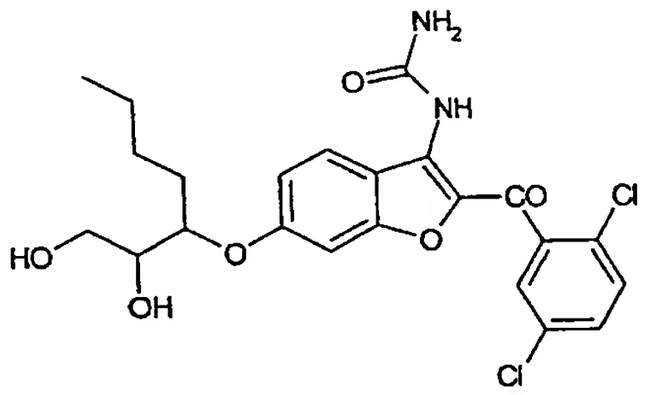
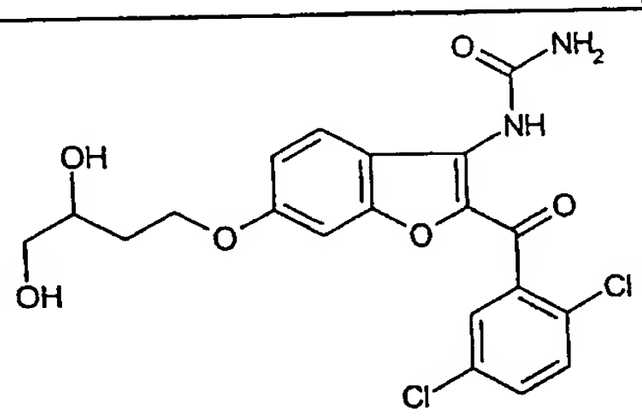
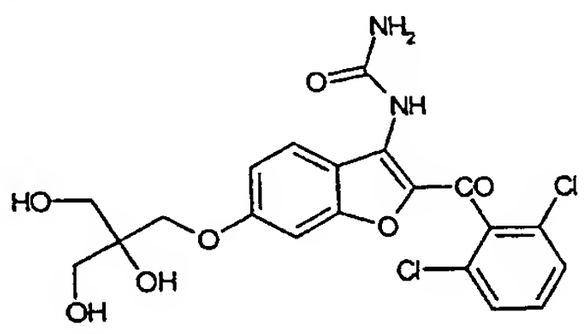
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
10		RACEMATE	186-7	48	
11		RACEMATE	150-2	61	
12		RACEMATE	184-6	90	
13		MIXTURE OF DIASTEREOMERS	115-7	94	

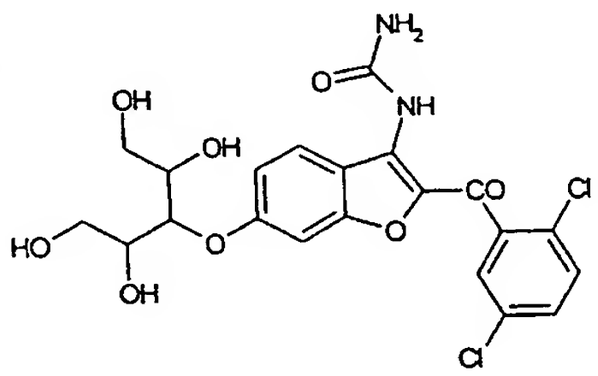
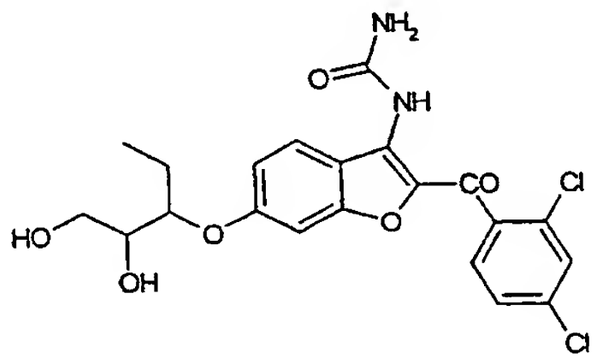
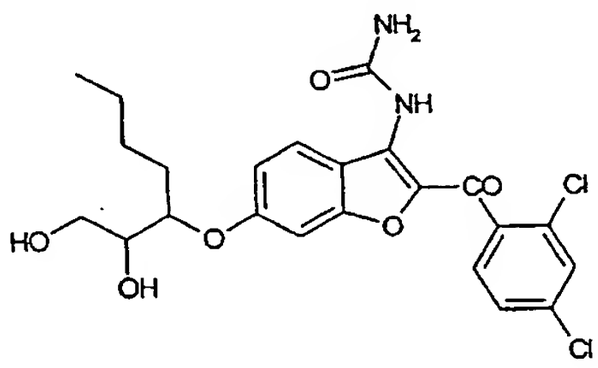
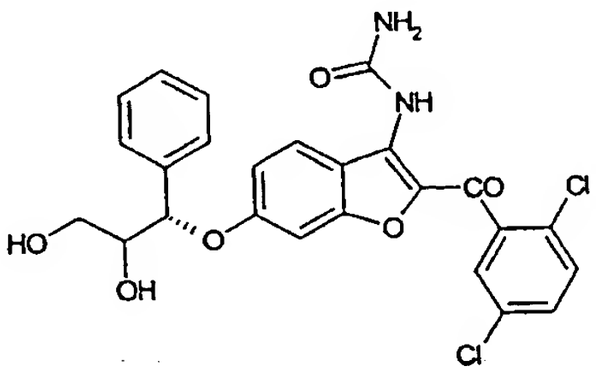
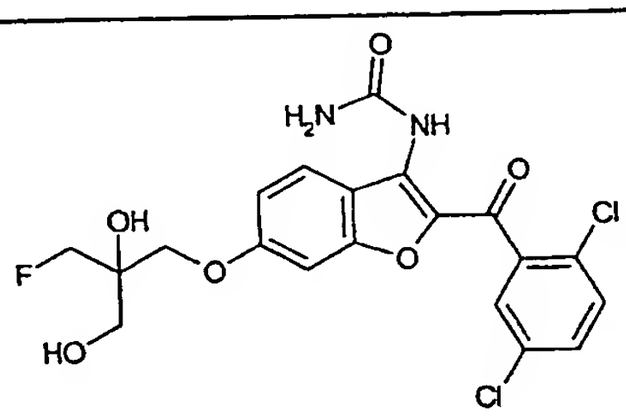
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
14			175	43	
15		RACEMATE	211	70	0.46 [d]
16			137-8	98	
17		(R)-ENANTIOMER OF Ex.-No. 12	204-5		
18			208	64	0.46 [d]

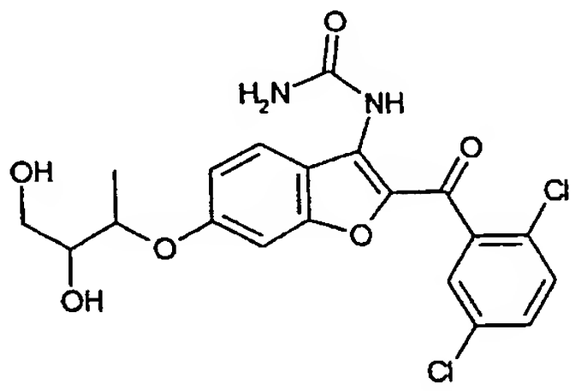
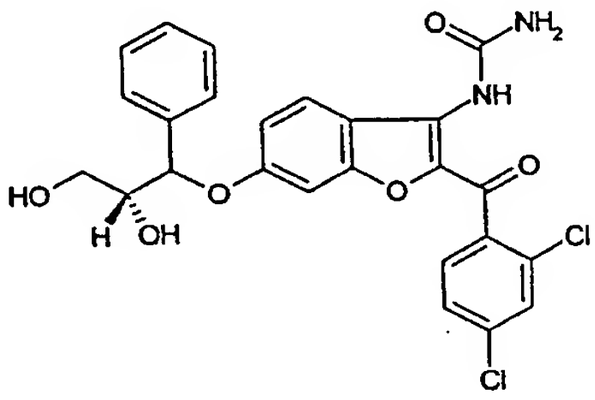
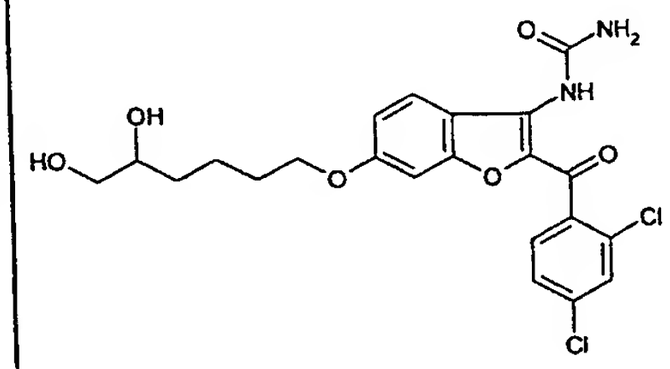
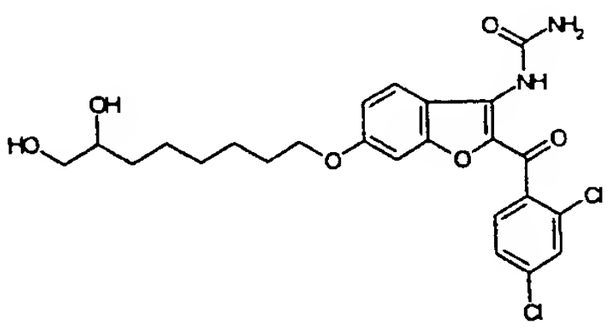
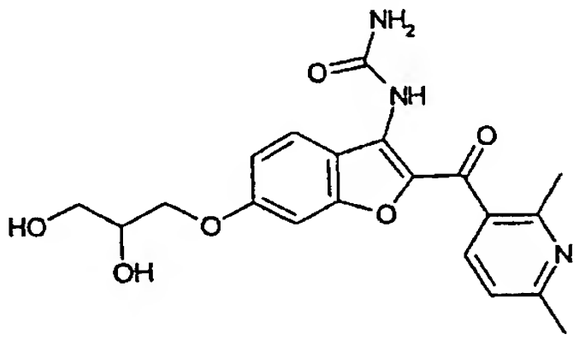
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
19			224	90	0.52 d)
20		ENANTIOMER A OF Ex.-No. 10	192		
21		ENANTIOMER B OF Ex.-No. 10	192		
22			223	15	0.16 a)

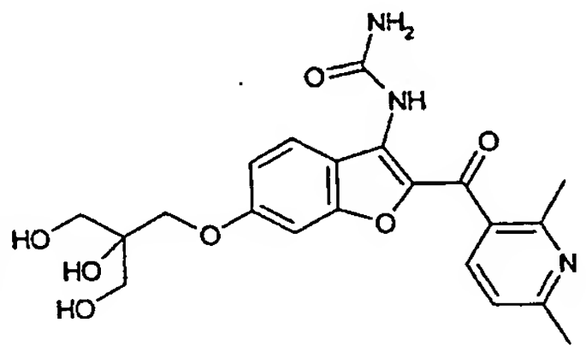
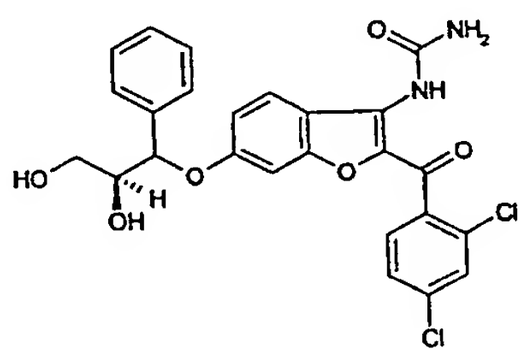
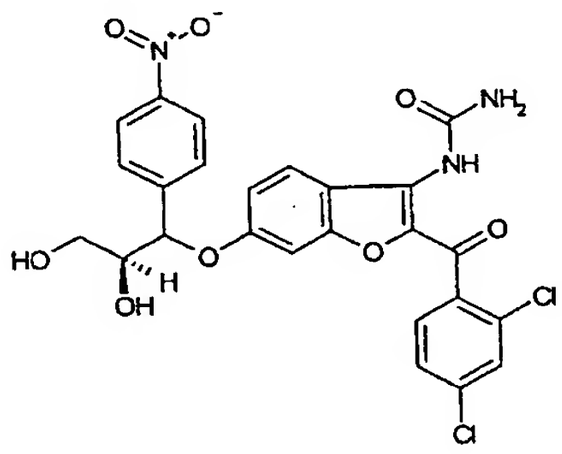
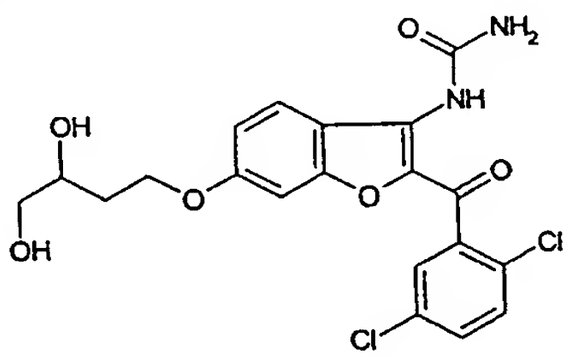
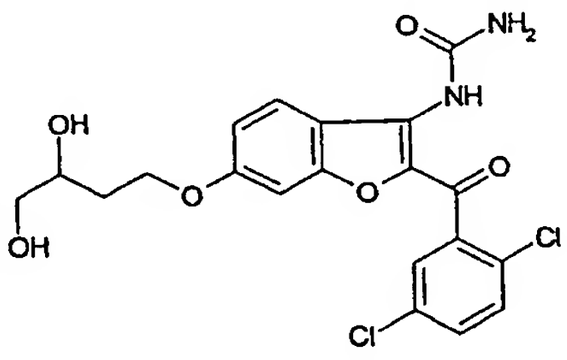
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
23			179-83	25	0,33 a)
24		MIXTURE OF DIASTEREOMERS	163		
25			218	50	
26		R-ENANTIOMER	116-8	32	

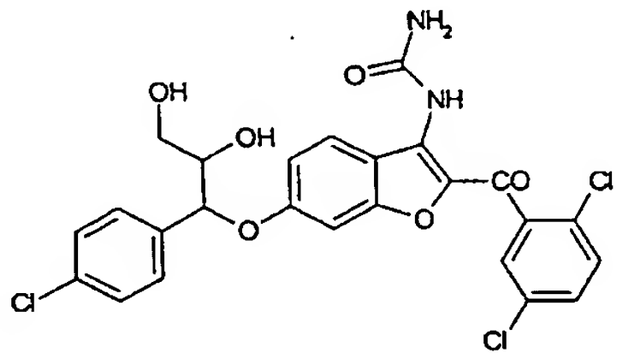
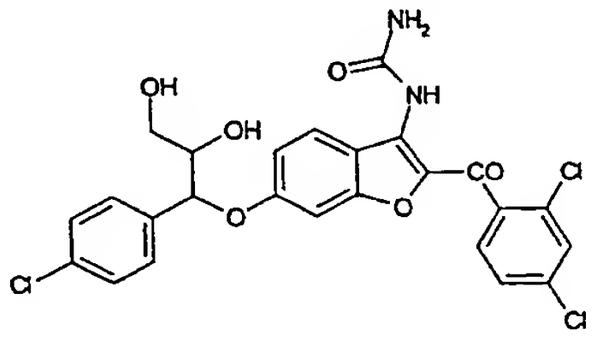
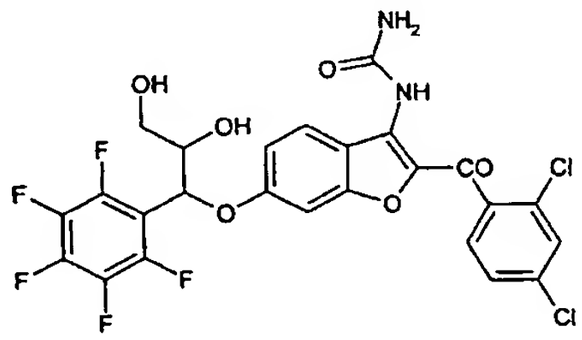
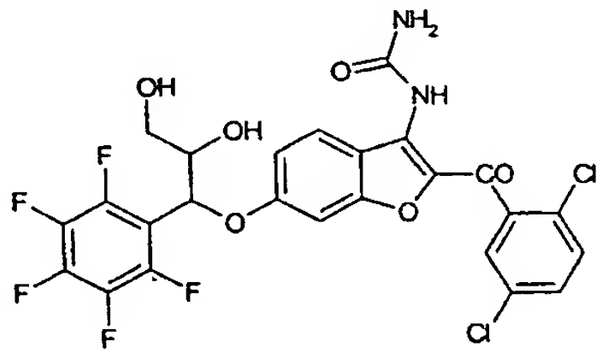
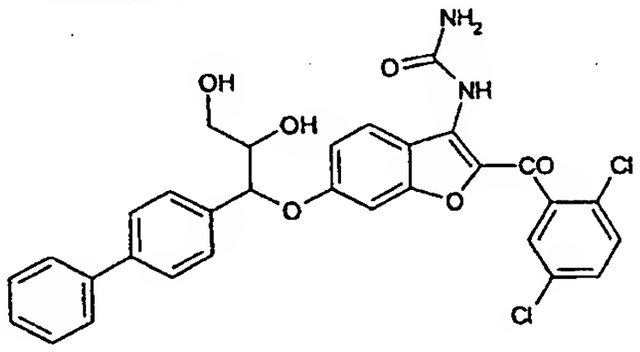
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
27		DIASTEREOMER A	125		
28		DIASTEREOMER B	125		
29		DIASTEREOMER A	130	27	0.40 [d]
30		MIXTURE OF DIASTEREOMERS	110-120	60	0.30 - 0.40 [d]

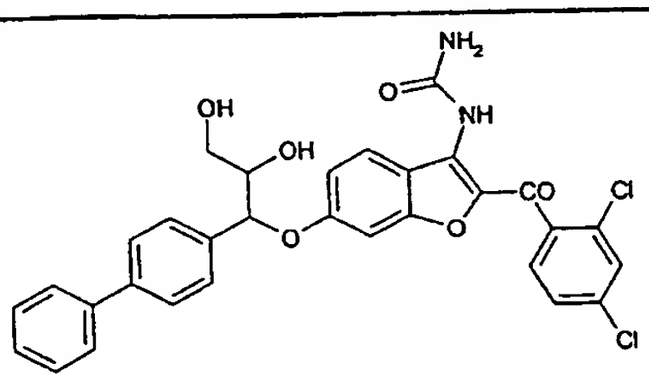
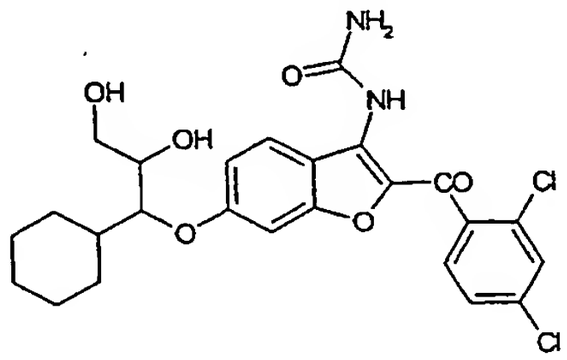
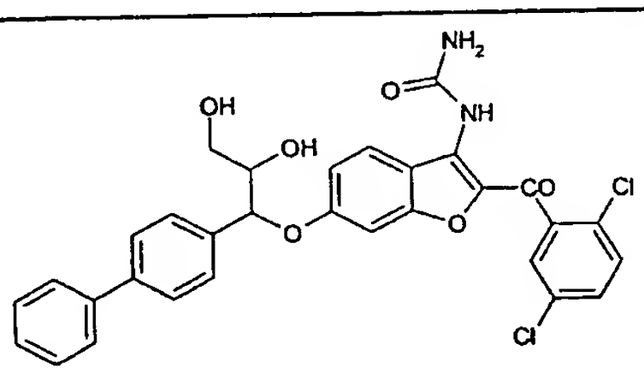
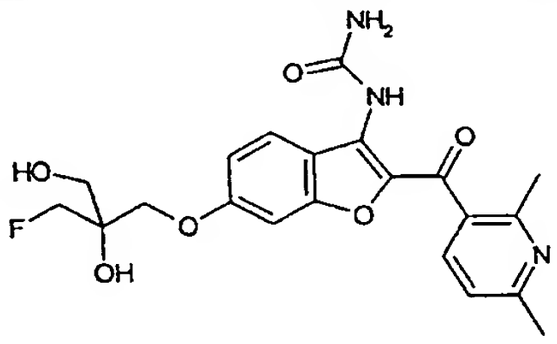
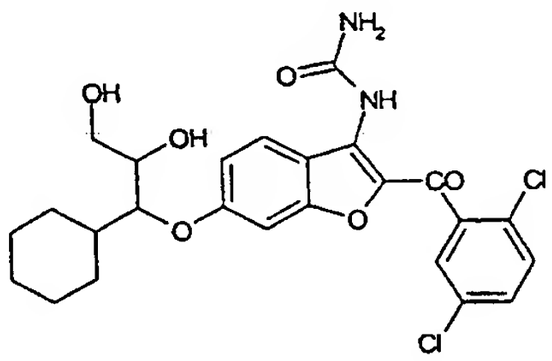
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
31		MIXTURE OF DIASTEREOMERS	130-3	30	0,16 b)
32		MIXTURE OF DIASTEREOMERS	92-120	65	0,16 (b)
33		MIXTURE OF DIASTEREOMERS	98-108	68	0,2 (b)
34		RACEMATE	198-9	94	
35			216-218	78	0,14 (a)

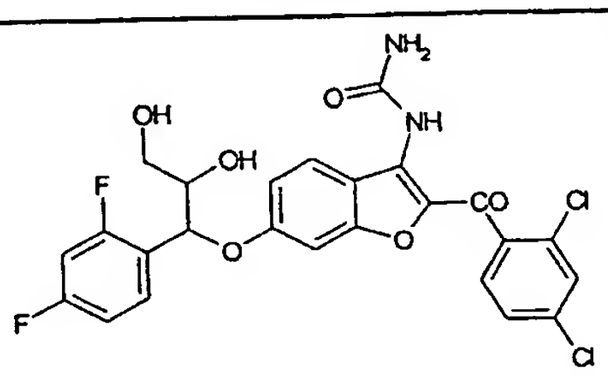
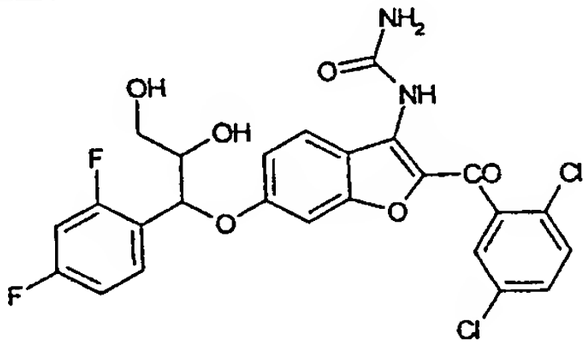
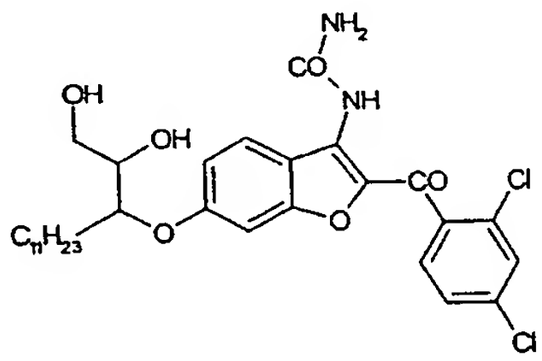
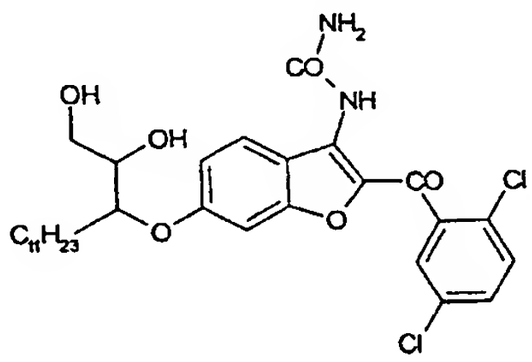
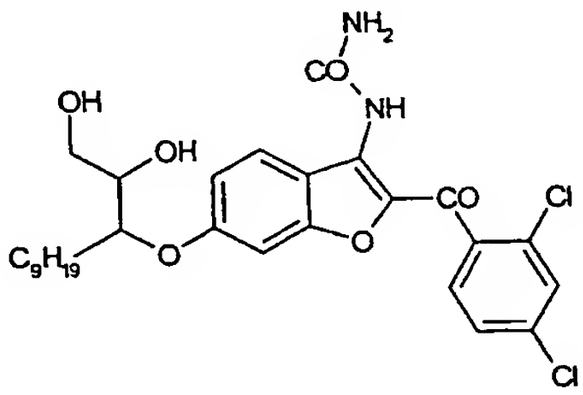
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
36			170-80	20	0,02 (b)
37		MIXTURE OF DIASTEREOMERS	107	83,5	0,14 (c)
38			153-9	84	0,1 (b)
39		DIASTEREOMER A	231	50	0,6 (a)
40		RACEMATE	191-2	25	

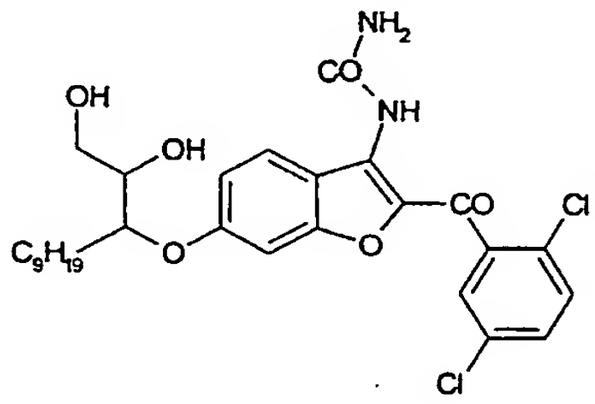
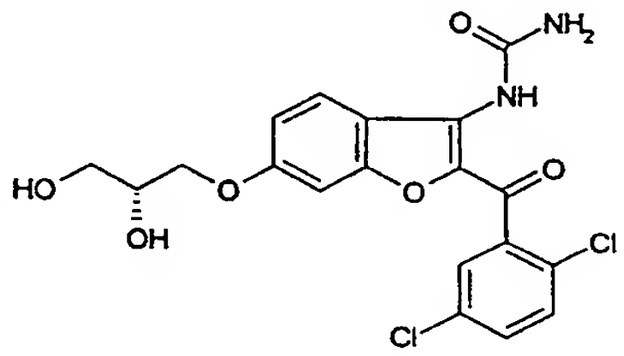
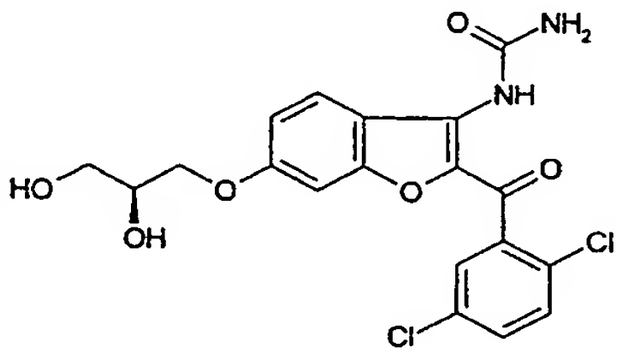
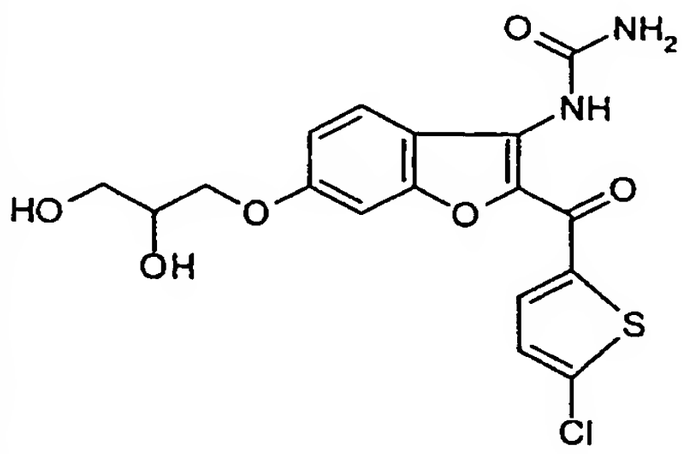
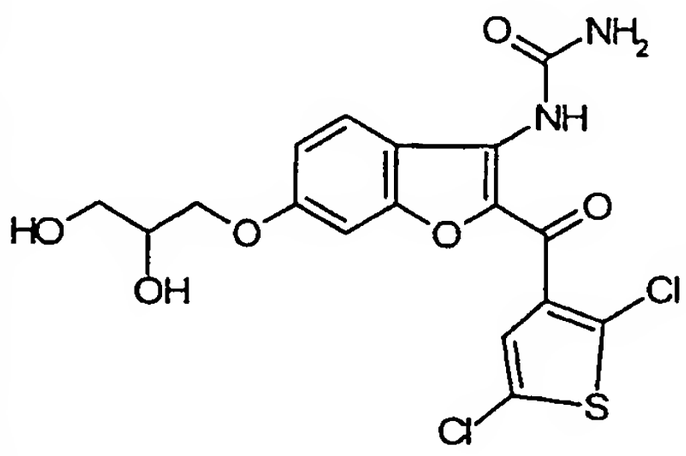
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
41		MIXTURE OF DIASTEREOMERS	115-6	71	
42		DIASTEREOMER A	122	13	
43		RACEMATE	115-6	89	
44		RACEMATE	134-5	81	
45				67	0.25 (i)

Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
46				quant.	0.12 (i)
47		DIASTEREOMER B	140-1	16	
48		DIASTEREOMER A	102-3	6	
49		ENANTIOMER A OF Ex.-No. 34	198-9	13	
50		ENANTIOMER B OF Ex.-No. 34	198-9	15	

Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
51		DIASTEREOMER A	105 (dec.)	30	0.88 [d]
52		DIASTEREOMER A	110	40	0.72 [d]
53		DIASTEREOMER A	136	8	0.86 [d]
54		DIASTEREOMER A	115 - 120 (dec.)	10	0.82 [d]
55		DIASTEREOMER A	116-124	20	0.68 [d]

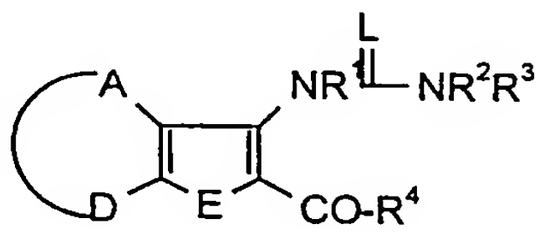
Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
56		DIASTEREOMER A	130 (dec.)	20	0.70 [d]
57		DIASTEREOMER A	170 (dec.)	7	0.20 [e]
58		MIXTURE OF DIASTEREOMERS	102-110	25	0.65 - 0.70 [d]
59				46	0.2 [i]
60		MIXTURE OF DIASTEREOMERS		10	0.20 - 0.26 [c]

Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
61			200 (dec.)	22	0.80 d)
62		DIASTEREOMER A	133-140	20	0.74 d)
63		DIASTEREOMER A	152-154	22	0.28 f)
64		MIXTURE OF DIASTEREOMERS		10	0.29 f)
65		DIASTEREOMER A		38	0.16 f)

Ex.-No.	Structure	isomer	mp. (°C)	yield (% of th.)	Rf *
66		MIXTURE OF DIASTEREOMERS		15	0.72 [d]
67		R (+) ENANTIOMER	200	18	0.46 [d]
68		S(-)-ENANTIOMER	205	23	0.46 [d]
69		RACEMATE	209-214	95	0.26 [d]
70		RACEMATE	200	42	0.35 [d]

We claim:

1. Oligohydroxyl 3-urea-benzofurane- and pyridofurane-derivatives of the general formula (I)



(I)

in which

A and D including the double bond connecting them together form a phenyl-, pyridyl-, pyrimidyl, pyridazinyl-, pyrazinyl- or thienyl-ring, which is substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having 1 to 15 carbon atoms, which is substituted difold to fivefold by hydroxyl or di-fold to fivefold by straight-chain oder branched alkoxy having 1 to 6 carbon atoms and wherein alkyl is optionally substituted by straight-chain or branched alkoxycarbonyl having 1 to 6 carbon atoms, halogen, carboxyl, (C_3-C_8)-cycloalkyl or by phenyl, which is optionally substituted monofold to fivefold by nitro, halogen or phenyl,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms, an aminoprotecting group or a group of the formula -CO-R^6

in which

R^6 denotes straight chain or branched alkoxy having 1 to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cycloalkyl having 3, 4, 5 or 6 carbon atoms, straight chain or branched alkyl, alkoxycarbonyl or alkenyl each having 1 to 8 carbon atoms,

or

R^2 and R^3 together with the nitrogen atom form a 5-, 6- or 7-membered saturated heterocycle optionally having a further oxygen atom,

R^4 represents aryl having 6 to10 carbon atoms or

represents a 5-, 6- or 7-membered, aromatic, saturated or unsaturated heterocycle, which can contain 1 to 3 oxygen, sulphur and/or nitrogen atoms as heteroatoms or a residue of a formula -NR^7,

wherein

R^7 denotes hydrogen or straight-chain or branched alkyl or alkoxycarbonyl each having 1 to 6 carbon atoms,

and to which further a benzene ring can be fused and wherein aryl and/or the heterocycle are optionally monosubstituted to trisubstituted

by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having 1 to 6 carbon atoms or by straight-chain or branched alkyl having 1 to 5 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having 1 to 4 carbon atoms or by a group of formula $-NR^8R^9$, $-SR^{10}$, $-(NH)_a-SO_2R^{11}$ or $-O-SO_2R^{12}$,

in which

R^8 and R^9 are identical or different and denote hydrogen or a straight-chain or branched alkyl having 1 to 4 carbon atoms,

or

R^8 denotes hydrogen

and

R^9 denotes straight-chain or branched acyl having 1 to 6 carbon atoms,

R^{10} denotes hydrogen or straight-chain or branched alkyl having 1 to 4 carbon atoms,

a denotes a number 0 or 1,

R^{11} and R^{12} are identical or different and represent straight-chain or branched alkyl having 1 to 6 carbon atoms, benzyl or phenyl,

which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having 1 to 4 carbon atoms,

L represents an oxygen or sulfur atom

and salts thereof.

2. Compounds according to claim 1,

in which

A and D, including the double bond connecting them form together a phenyl-, pyridyl- or pyrimidyl-ring, which are substituted by a group of a formula $-OR^5$

wherein

R^5 denotes straight-chain or branched alkyl having 1 to 14 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by methoxy, ethoxy, n-propoxy, isopropoxy, fluorine, chlorine, cyclopentyl, cyclohexyl or by phenyl, which is optionally substituted monofold to fivefold by nitro, fluorine or chlorine or phenyl,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, straight-chain or branched alkyl having 1 to 4 carbon atoms or a group of the formula $-CO-R^6$

in which

R^6 denotes straight chain or branched alkoxy having 1 to 4 carbon atoms,

R^2 and R^3 are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having 1 to 4 carbon atoms, or

or

R^2 and R^3 together with the nitrogen atom form a pyrrolidinyl-, piperidinyl- or morpholinyl-ring,

and

R^4 represents phenyl, pyridyl or thienyl, wherein all rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having 1 to 3 carbon atoms, or by straight-chain or branched alkyl having 1 to 3 carbon atoms, which is optionally substituted by carboxyl or methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl or iso-propoxycarbonyl,

L represents an oxygen or sulfur atom,

and salts thereof.

3. Compounds according to claim 1 or 2,

in which

A and D, including the double bond connecting them form together a phenyl- or pyridyl-ring, which are substituted by a group of a formula -OR^5

wherein

R^5 denotes straight-chain or branched alkyl having 1 to 11 carbon atoms, which is substituted difold to fourfold by hydroxyl, and wherein alkyl is optionally substituted by methoxycarbonyl, cyclohexyl, fluorine or by phenyl, which is optionally substituted monofold to fivefold by nitro or fluorine or phenyl,

E represents an oxygen or sulfur atom,

R^1 represents hydrogen, methyl, ethyl, n-propyl, isopropyl or a group of the formula -CO-R^6,

in which

R^6 denotes denotes methoxy, ethoxy, n-propoxy or isopropoxy,

R^2 and R^3 represent hydrogen,

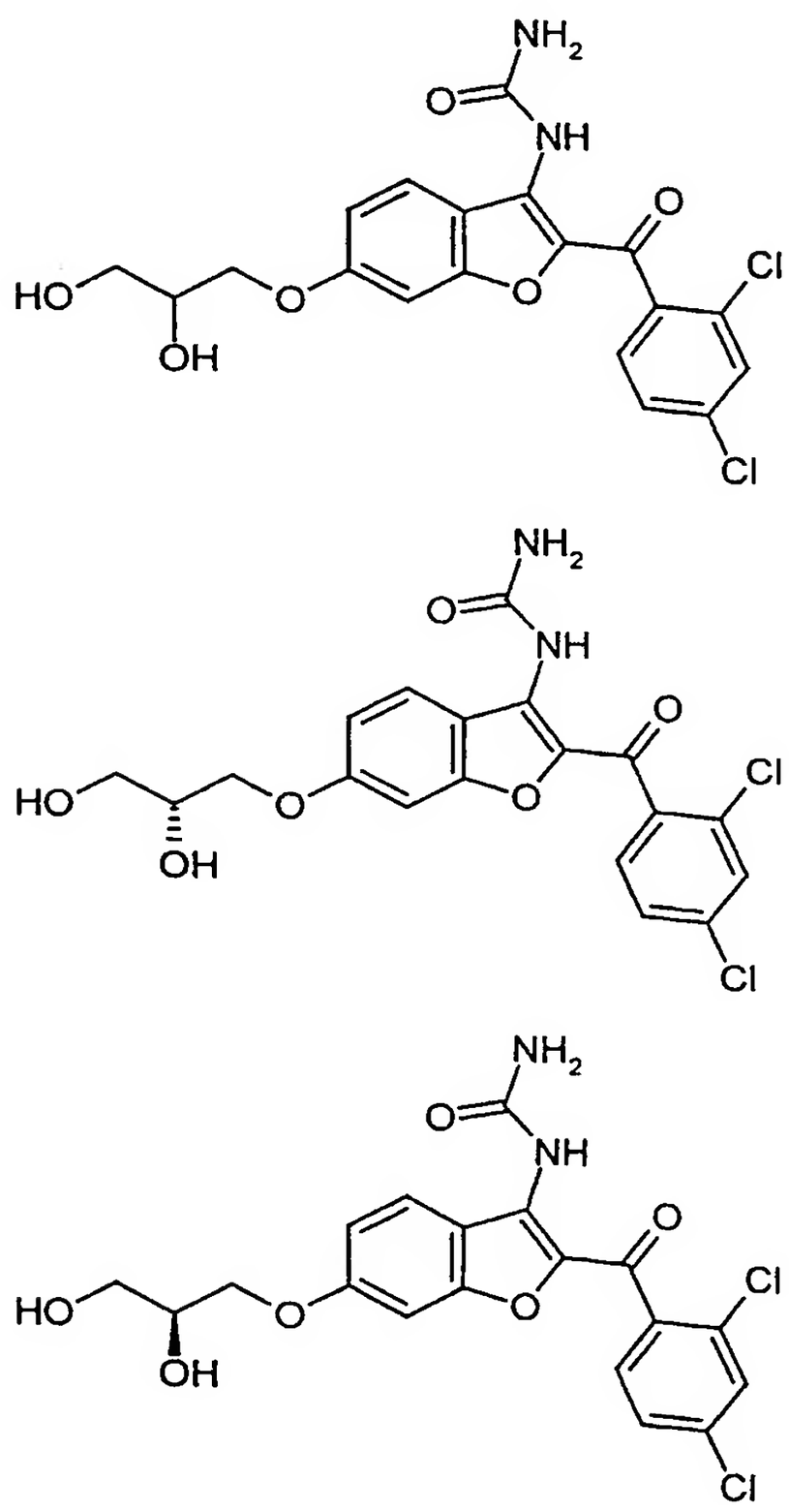
R^4 represents phenyl, pyridyl or thienyl, which are optionally up to trifold substituted by identical or different substituents from the series chlorine or methyl,

L represents an oxygen atom,

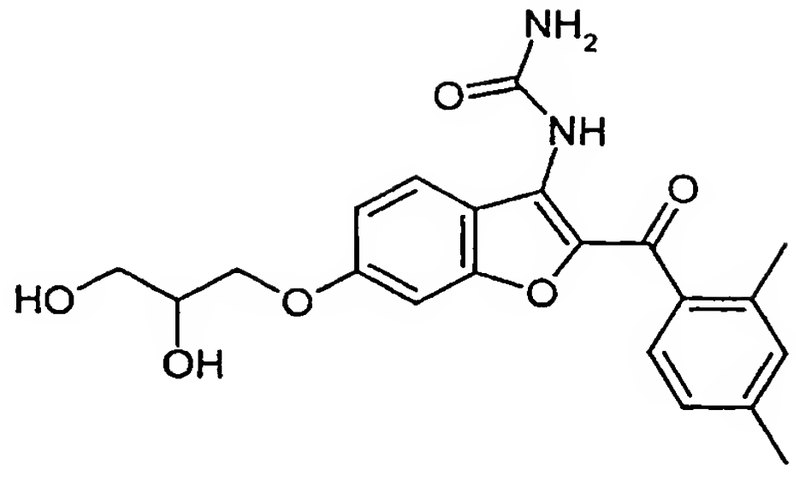
and salts thereof.

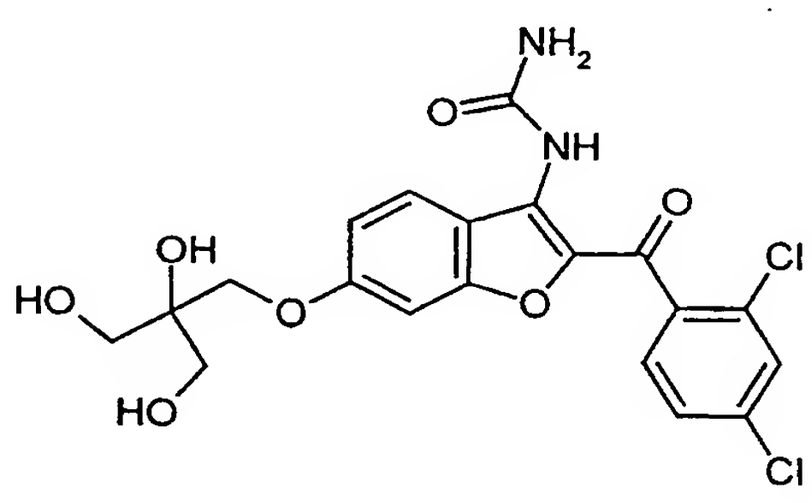
4. Compounds according to anyone of claims 1 to 3, selected from the following group:

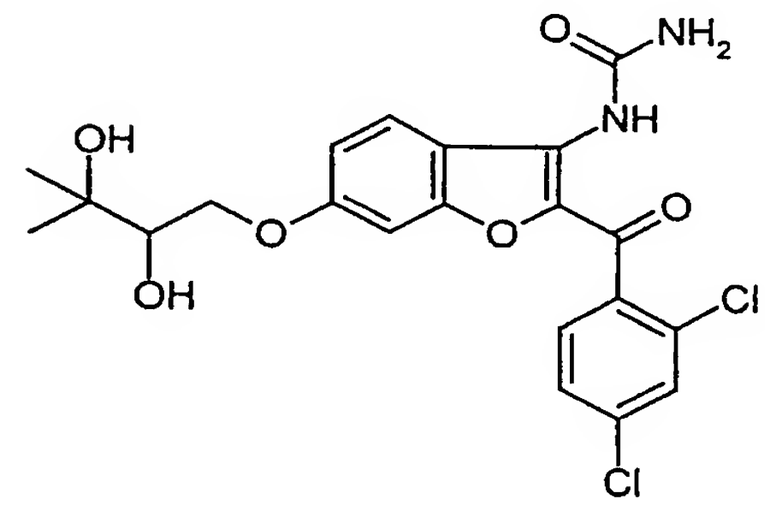
Structure

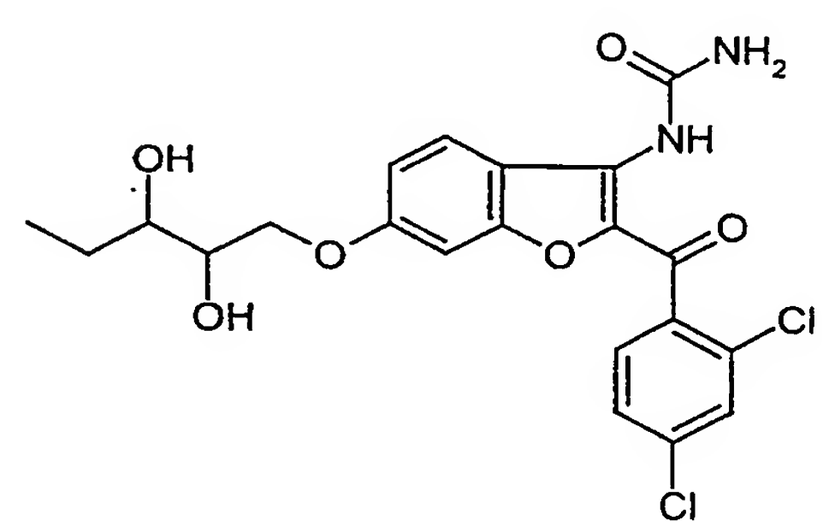


Structure

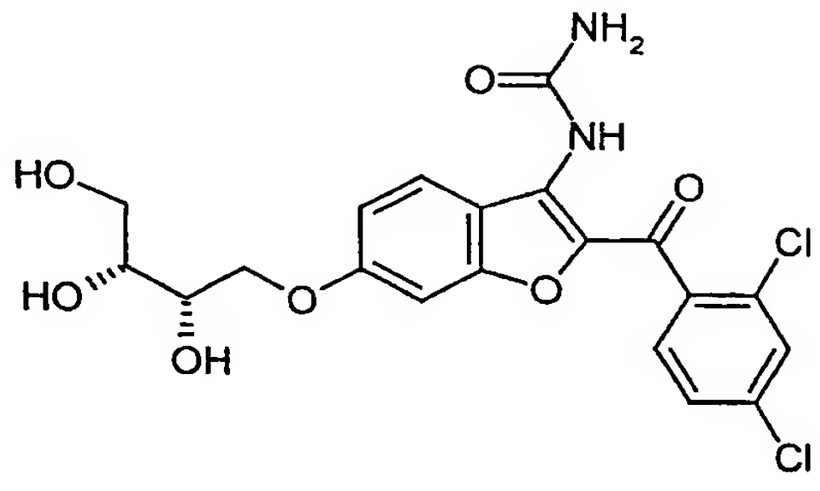


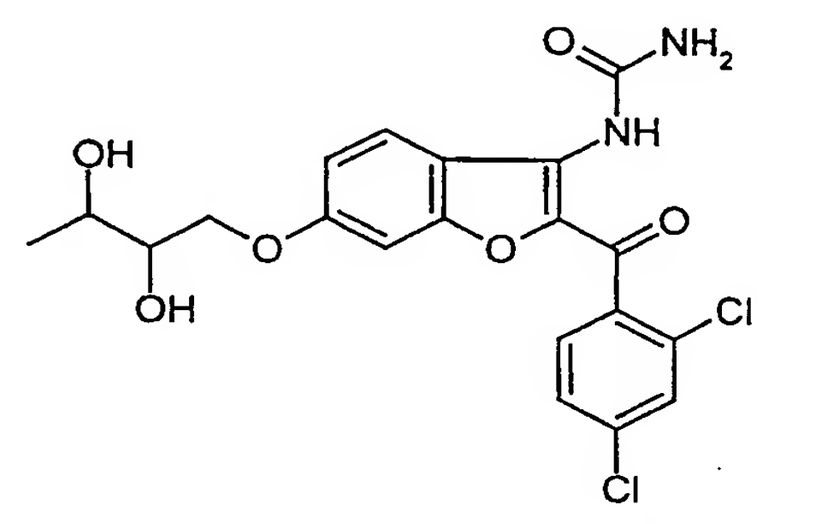


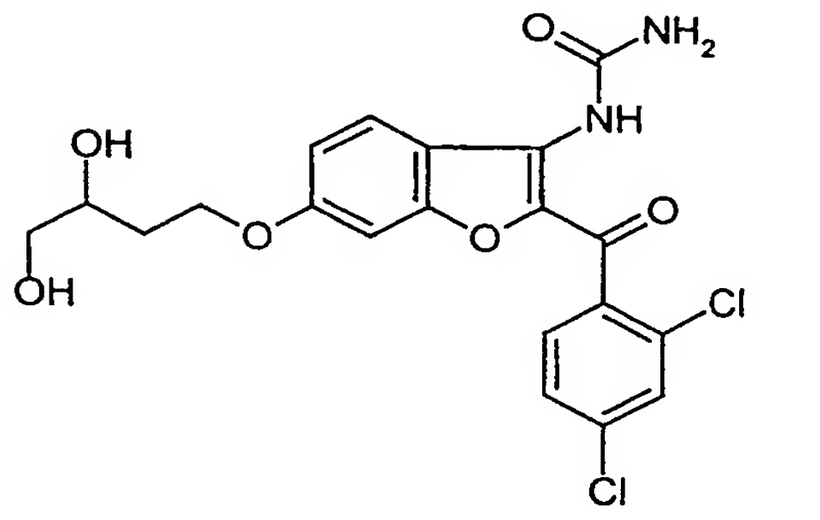


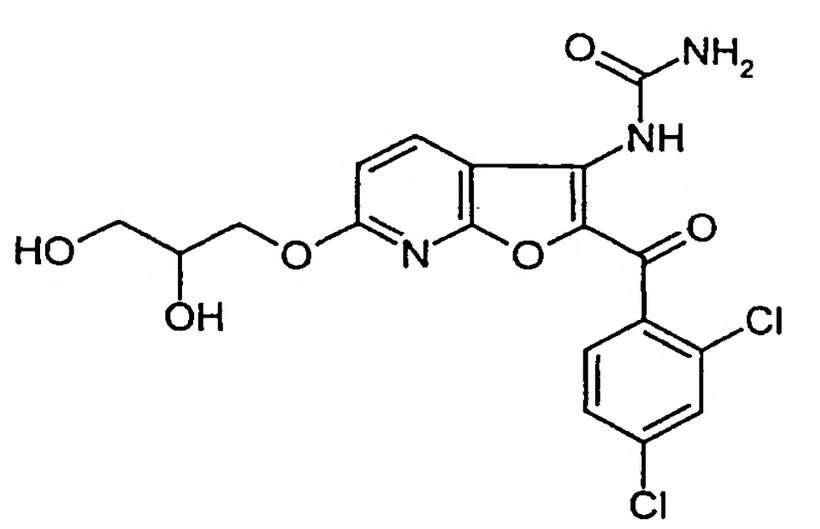


Structure









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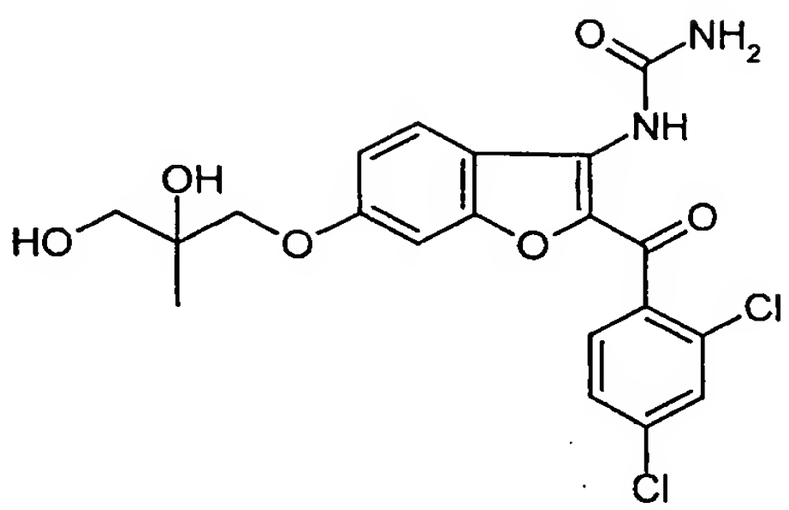

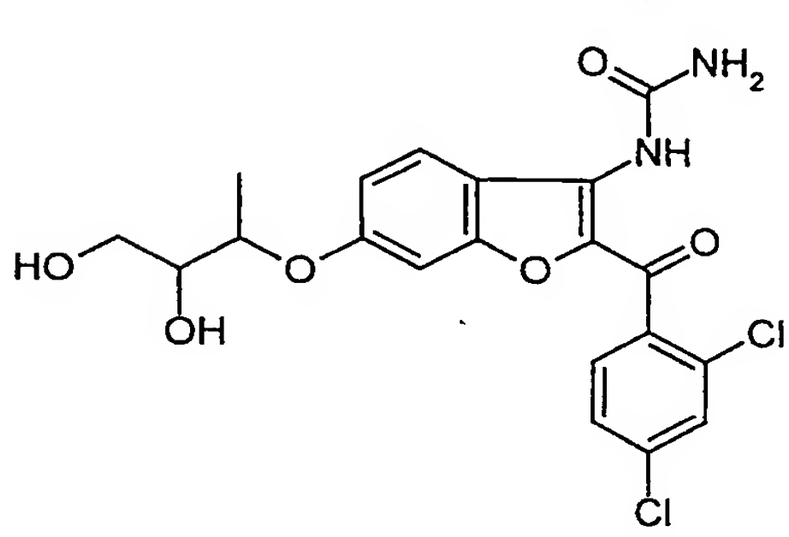

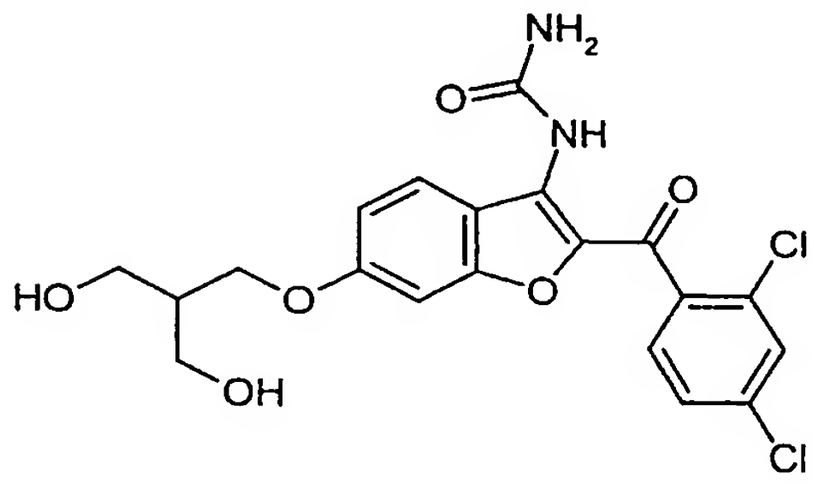

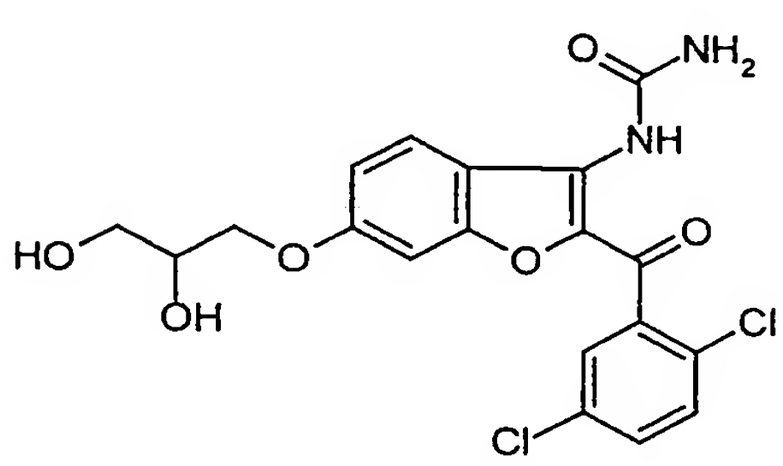

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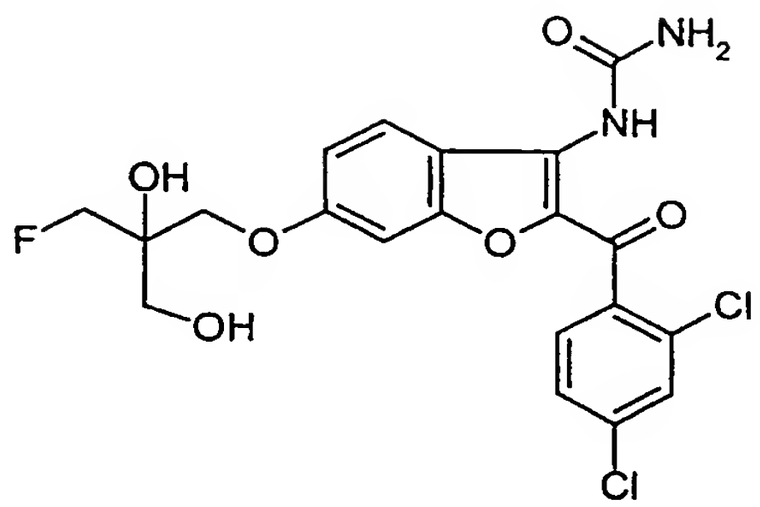

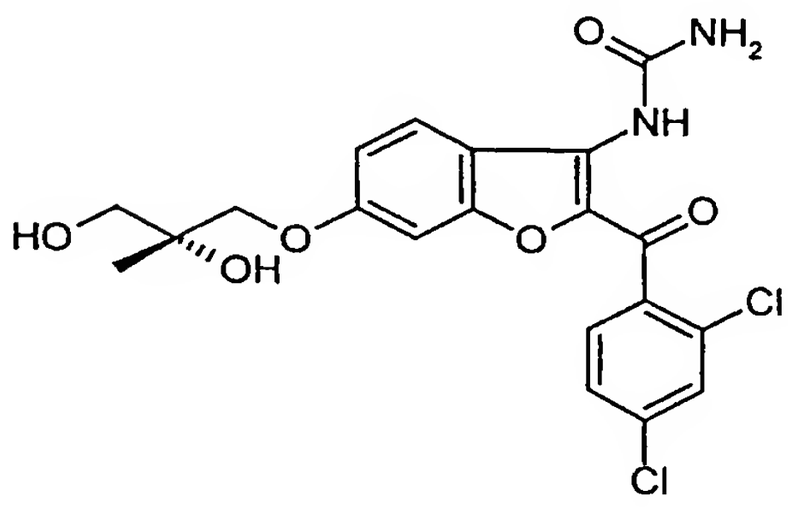

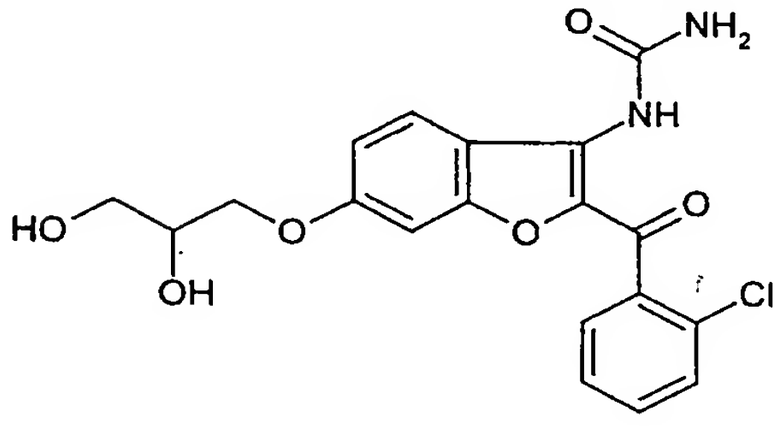

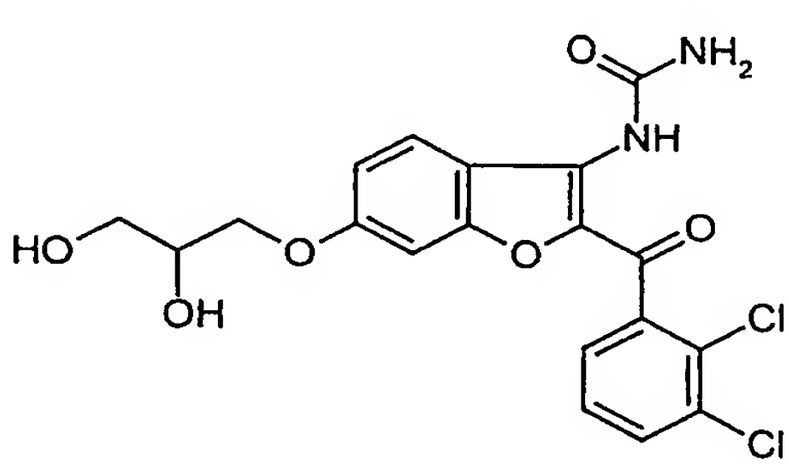

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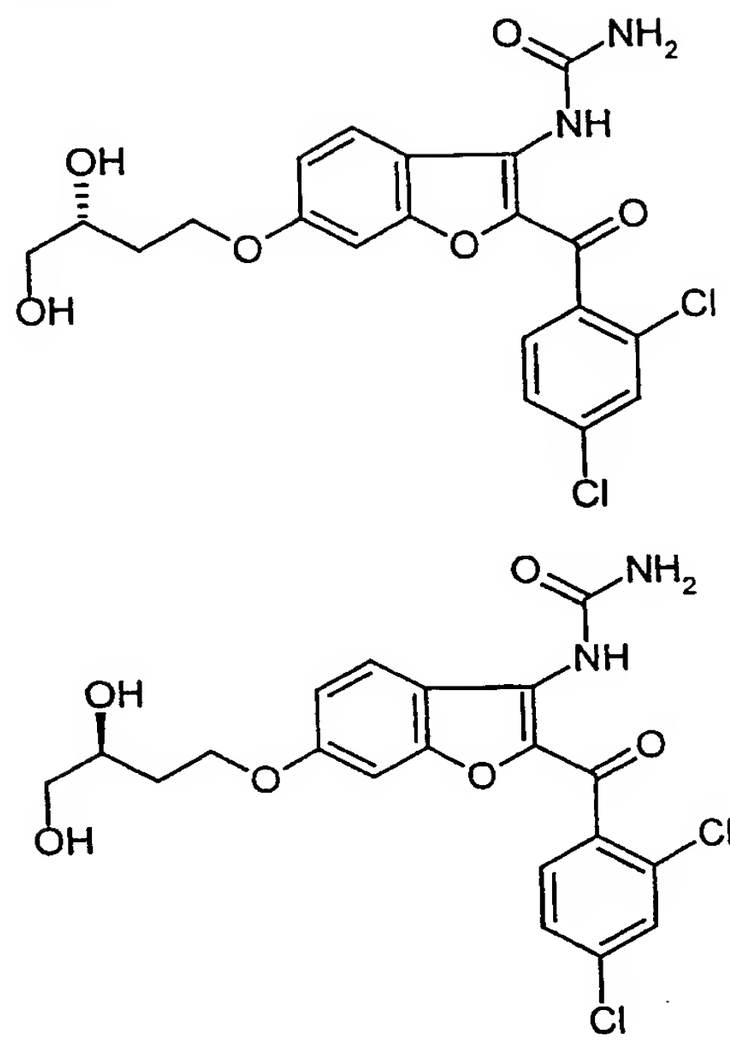

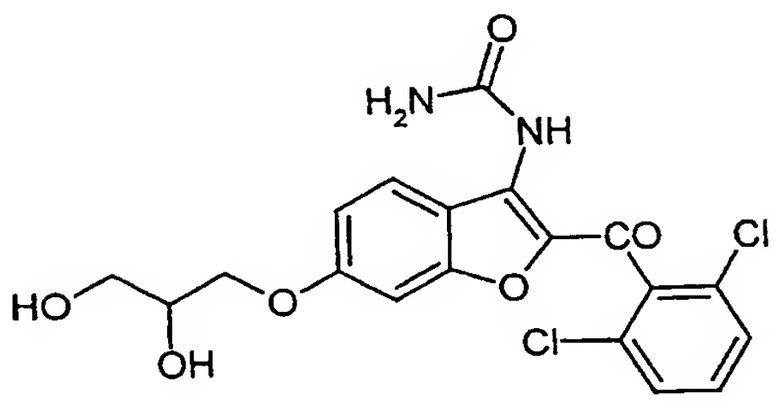

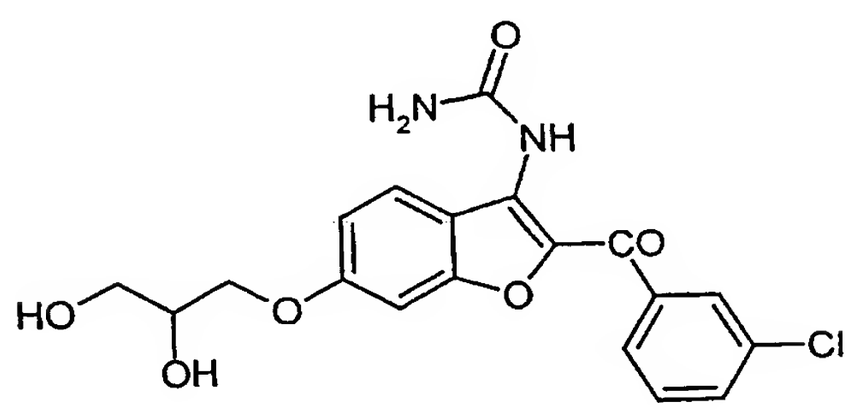

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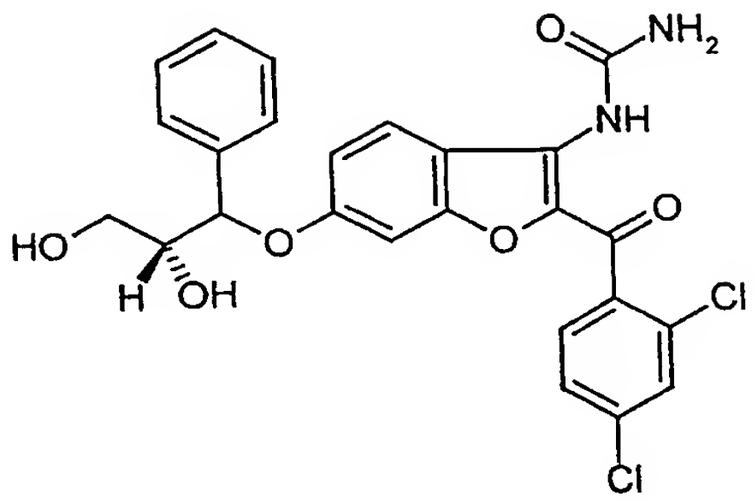

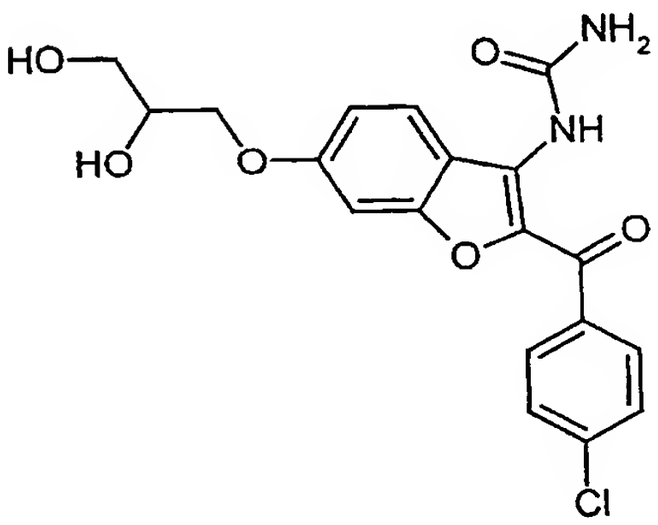

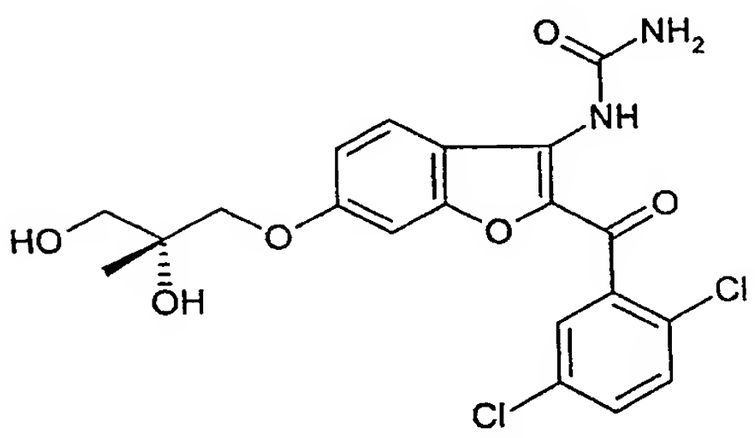

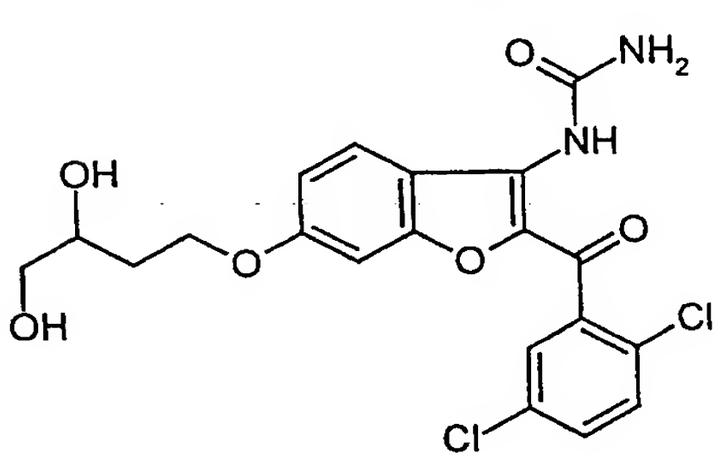

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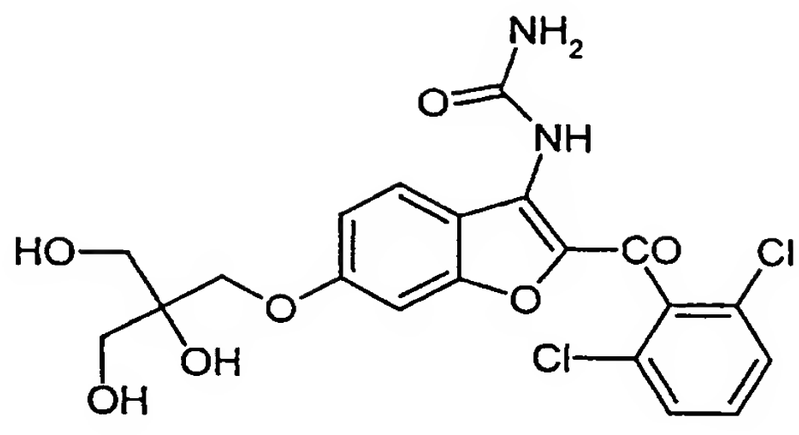

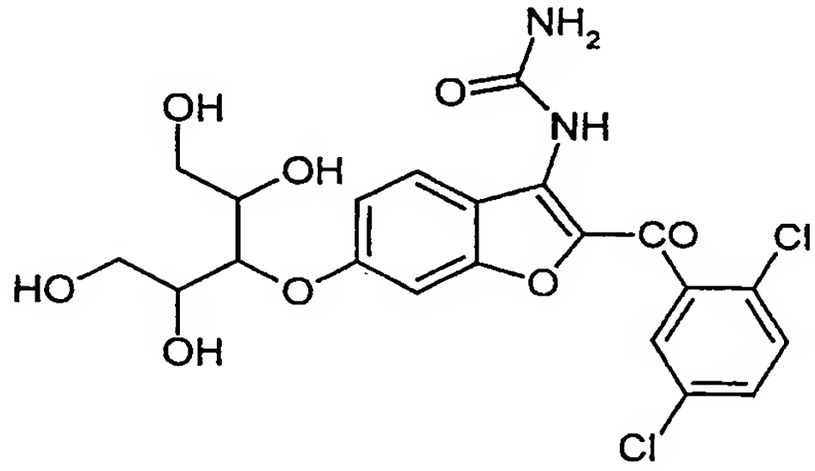

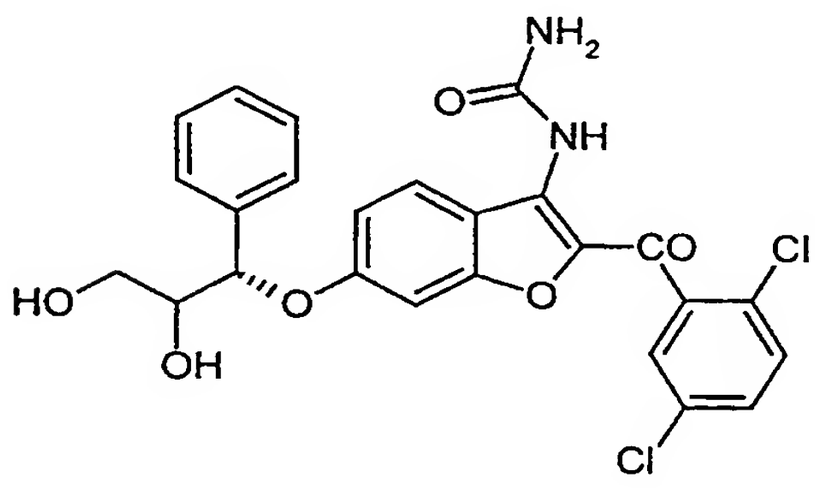

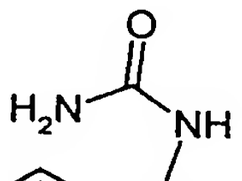

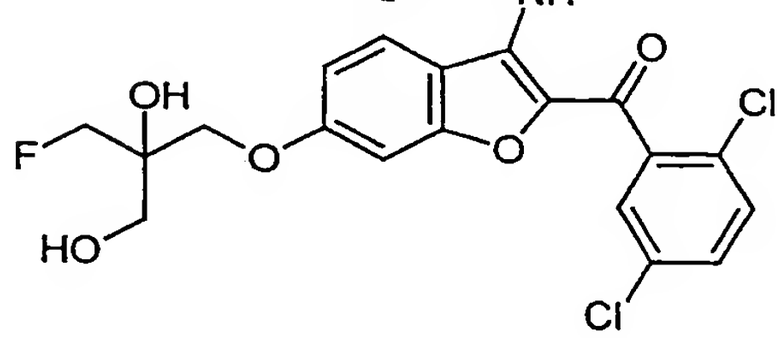

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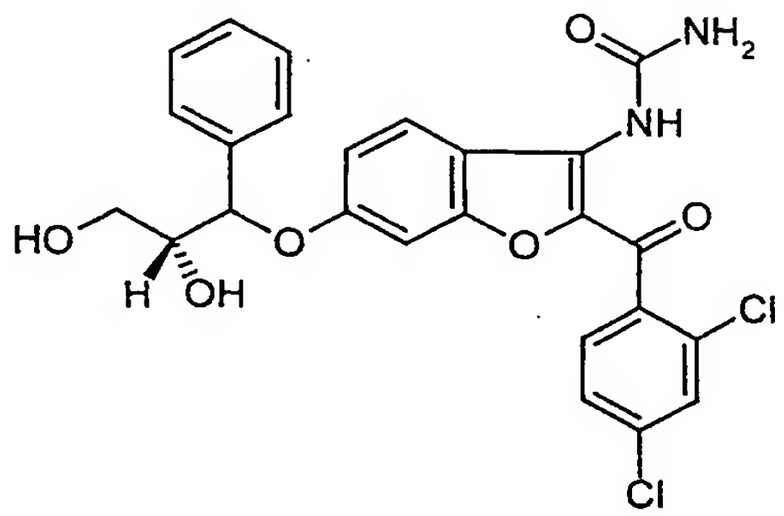

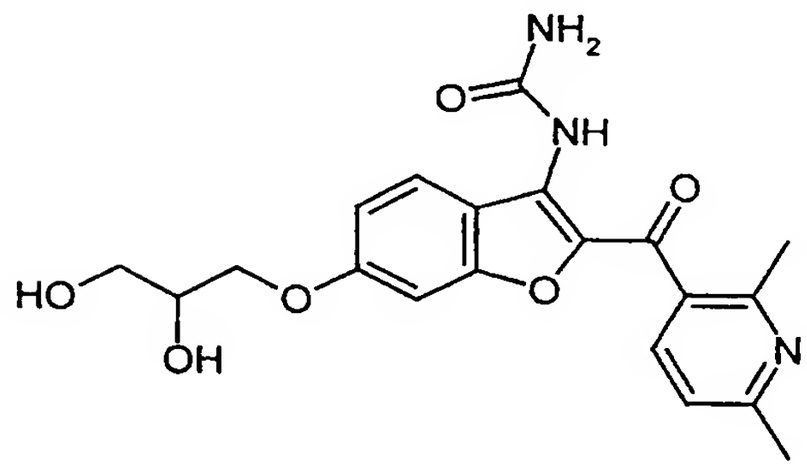

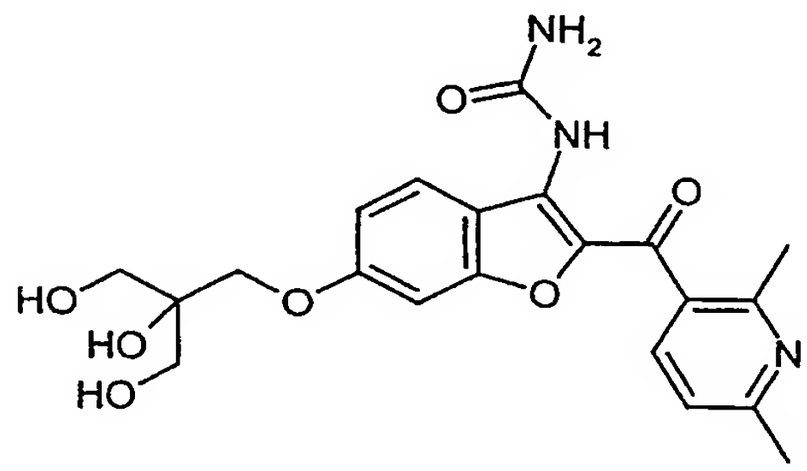

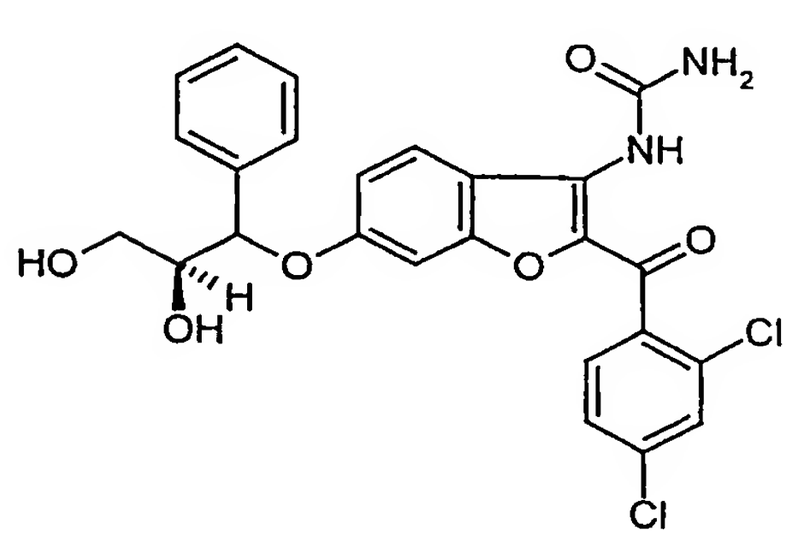

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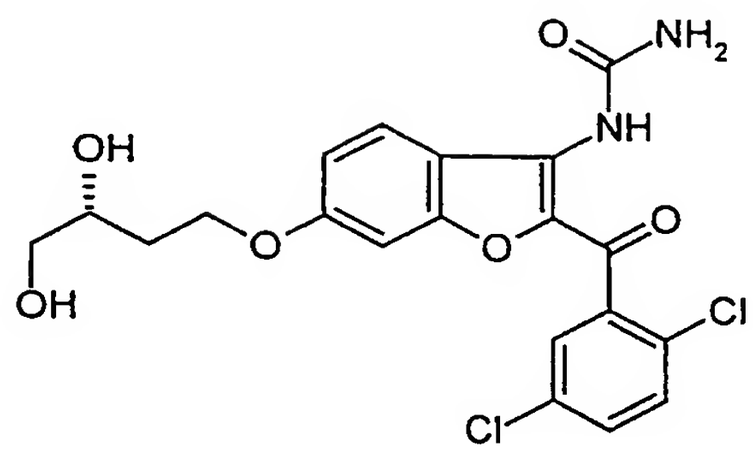

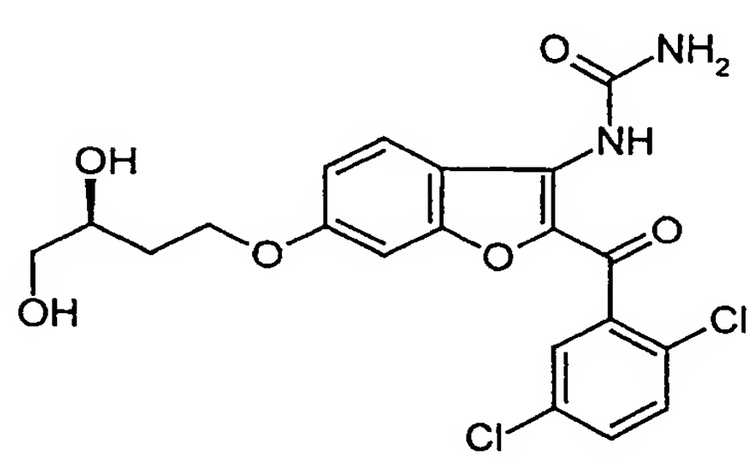

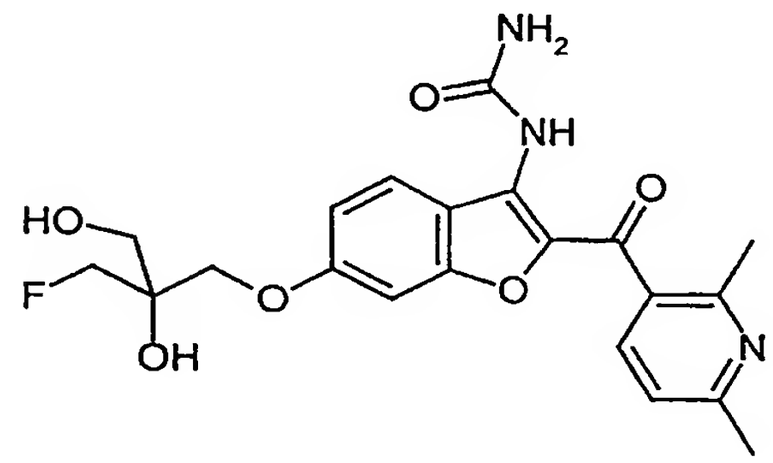

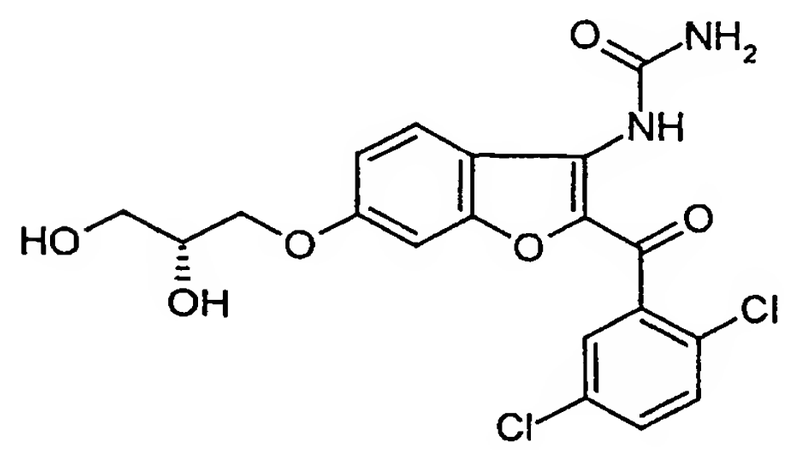

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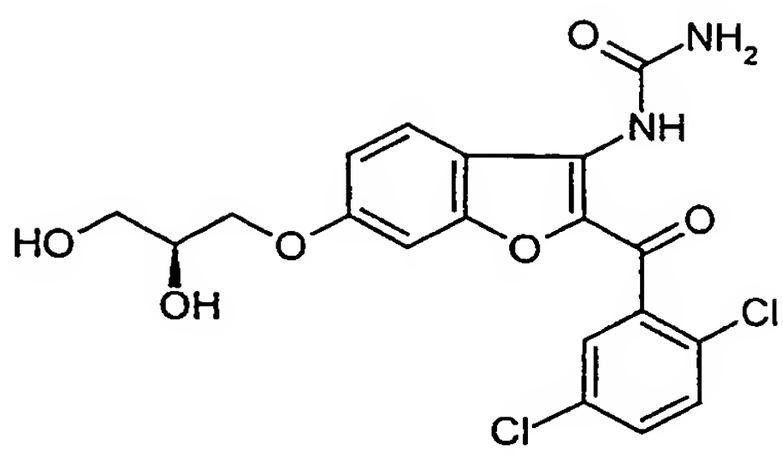
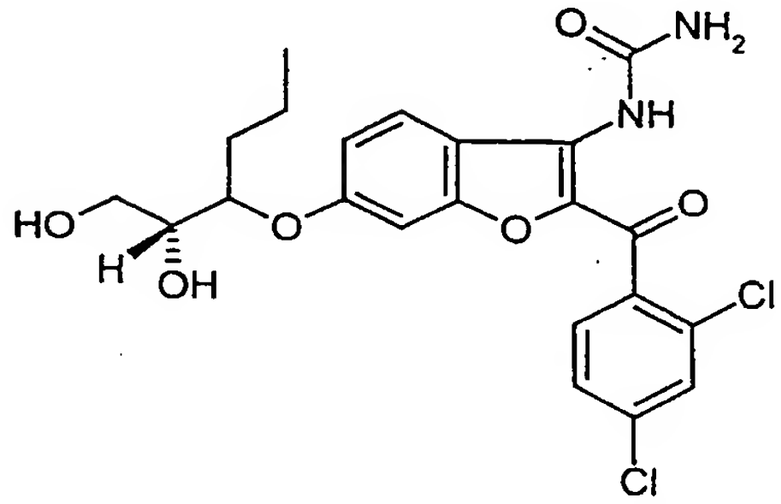
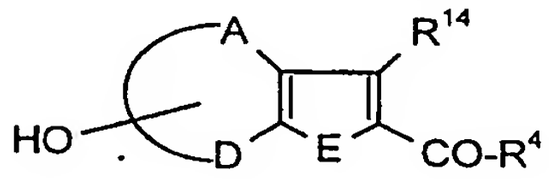




5. A process for the preparation of the compounds of the general formula (I) characterized in that,

that in the case in which R^5 denotes alkyl substituted by two vicinal hydroxyl-groups

[A] compounds of the general formula (II)



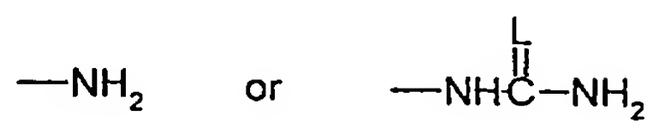
(II)

in which

R^4, A, D and E have the abovementioned meaning,

and

R^{14} denotes a residue of a formula



wherein L has the abovementioned meaning,

first are reacted with compounds of the general formula (III)

$$R^{15}\text{-}CH_2\text{-}Z' \qquad \text{(III)}$$

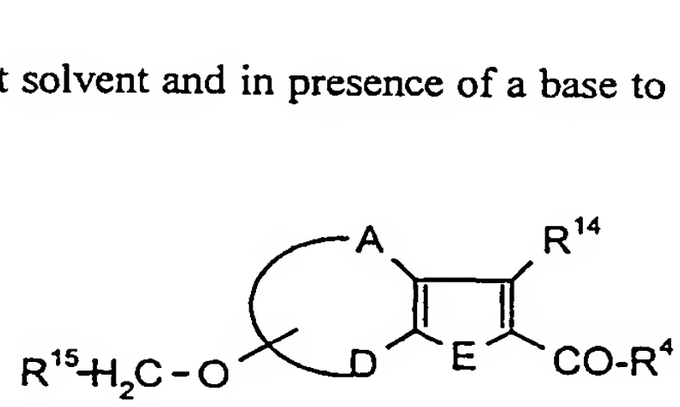
in which

R^{15} denotes straight-chain or branched alkenyl having 1 to 9 carbon atoms, which is optionally substituted by phenyl, biphenyl or optionally nitro- or halogen-substituted phenyl and/or halogen,

and

Z' denotes a leaving group such as mesyl, tosyl, chlorine, bromine or iodine

in inert solvent and in presence of a base to compounds of the general formula (IV)



(IV)

in which

A, D, E, R^4, R^{14} and R^{15} have the abovementioned meaning,

and in a last step are reacted with osmiumtetroxide (OsO_4)/N-methyl-morpholino-N-oxide in inert solvents,

or

in the case in which R^5 denotes alkyl substituted by two to five hydroxyl groups

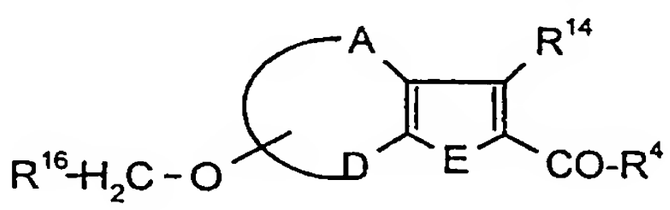
[B] compounds of the general formula (II) are reacted with compounds of the general formula (V)

$$R^{16}\text{-}CH_2OH \qquad (V)$$

in which

R^{16} denotes straight-chain or branched alkenyl having 1 to 9 carbon atoms, which is optionally substituted by hydroxyl,

in inert solvents and in the presence of triphenylphosphine / diethylazodicarboxylate to compounds of the general formula (VI)



(VI)

in which

A, D, E, R^4, R^{14} and R^{16} have the abovementioned meaning

and in a last step are reacted with OsO_4/N-methylmorpholino-N-oxide inert solvents,

or

[C] compounds of the general formula (II) are reacted with alcohols of the general formula (VII)

$$R^5\text{-}OH \qquad (VII)$$

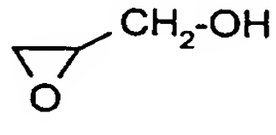
in which

R^5 has the abovementioned meaning

in inert solvents and in presence of triphenylphosphine / diethylazodicarb-oxylate

or

[D] compounds of the general formula (II) are reacted with the compound of the formula (VIII)



(VIII)

in inert solvents and in the presence of a base and titanium-(IV) isopro-pylate

and in the case

in which R^1, R^2 and/or $R^3 \neq H$ the free amino groups are derivated optionally by common methods.

6. Oligohydroxyl-substituted 3-urea-benzofurane- and -pyridofurane derivatives according to any one of claims 1 to 4 for therapeutic use.

7. The composition containing at least one oligohydroxyl 3-urea-benzofurane- or pyridofurane-derivative according to any one of claims 1 to 4 and a pharmacologically acceptable diluent.

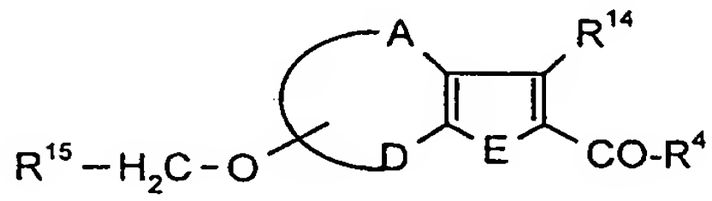
8. A composition according to claim 7, for the treatment and prevention of acute and chronic inflammatory processes.

9. The process for the preparation of compositions according to claim 7 and 8 characterized in that the oligohydroxyl-3-urea-benzofurane- or pyridofurane-derivative together with customary auxiliaries is brought into a suitable application form.

10. Use of oligohydroxyl 3-urea-benzofurane- or pyridofurane-derivatives according to anyone of claims 1 to 4 for the preparation of medicaments.

11. Use according to claim 10 for the preparation of medicaments for the treatment and prevention of acute and chronic inflammatory processes.

12. Oligohydroxyl substituted 3-urea-benzofurane and pyridofurane derivatives of the general formula (IV)

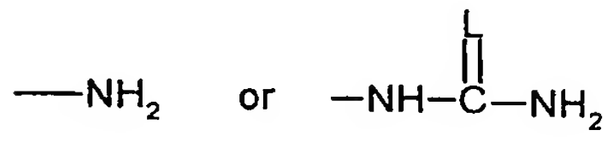


(IV)

in which

A, D, E and R^4 have the abovementioned meaning,

R^{14} denotes a residue of a formula



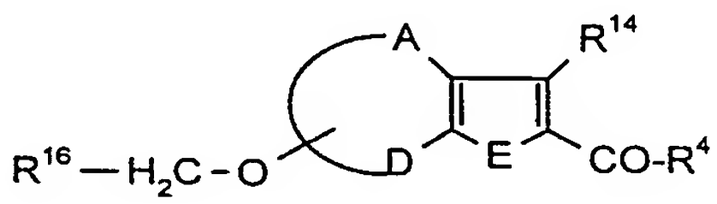
in which

L has the abovementioned meaning

and

R^{15} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by phenyl or nitro- or halogen-substituted phenyl and/or halogen.

13. Compounds of the generala formula (VI)



(VI)

in which

A, D, E, R^4 and R^{14} have the abovementioned meaning and

R^{16} denotes straight-chain or branched alkenyl having up to 9 carbon atoms, which is optionally substituted by hydroxyl.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 00/04016

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D307/82 C07D409/06 C07D491/048 C07D407/06 A61K31/34
A61K31/44 A61P29/00 //(C07D491/048,221:00,307:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 779 291 A (BAYER AG) 18 June 1997 (1997-06-18) claims 1-10 ---	1-10
Y	WO 98 02440 A (BAYER AG) 22 January 1998 (1998-01-22) claims 1-10 ---	1-10
Y	EP 0 731 099 A (BAYER AG) 11 September 1996 (1996-09-11) cited in the application claims 1-10 ---	1-10
Y	EP 0 146 243 A (MERCK FROSST CANADA INC.) 26 June 1985 (1985-06-26) claims 1-37 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 2000	28/08/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Herz, C

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 00/04016

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 623 607 A (BAYER AG) 9 November 1994 (1994-11-09) claims 1-9	1-10
Y	EP 0 685 479 A (BAYER AG) 6 December 1995 (1995-12-06) claims 1-10	1-10

1

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte onal Application No
PCT/EP 00/04016

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